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EIGHT YEARS' EXPERIENCE WITH THE ADRENAL GLAND

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Look at life as a whole—study its manifestations in order and disorder, in health and disease.—*Osler.*

INTRODUCTION

The most characteristic features of the medical profession, features which distinguish it from all the other walks in life, are its dedication to the service of mankind and its devotion to the spirit of research. Medicine is the only world-wide profession the members of which follow everywhere the same methods, actuated by the same ambitions and pursuing the same ends. Its strength lies in this universal doctrine, and although it may be tinged with national characteristics, in its wider aspects it is a force which knows no country, which transcends all national limitations and which acknowledges no distinction of race, color or creed and no sovereignty but that of the mind. Science has done much to alleviate the unhappy conditions in which so many persons live. All this has been achieved by research on man, the unit, and much remains to be done. The vast improvement in his status, politically, morally and socially, which has been the promethean gift of science during the past century, can be traced directly to the wider application of knowledge derived from the individual. But evolution advances by such slow and imperceptible steps that to those who are part of it the finger of time scarcely seems to move. Nevertheless, the medical profession continues to exercise such a monopoly in charity as to be able to dispense gargantuan gifts, for it is now possible that within a few weeks any great discovery is broadcast and is practiced everywhere. Even if the individual efforts of members of the profession are lilliputian, they travel on hopefully—it is better than to arrive, and their happiness is to labor. Sooner or later some one will arrive to construct a master picture from the multicolored pigments all have struggled to provide. The true student, therefore, must become a citizen of the world; he must have freedom of intercourse and access without restrictions, for ignorance of work done elsewhere is but so

much time wasted. The evil, however, which besets all such good intentions is the sapping of one's energies by the stress of routine work.

HISTORICAL DATA

Mythology, art and sculpture throughout the ages have been acquainted with and have portrayed curious anomalies of the characters of one sex appearing in the other, which have always given rise to much speculation. In ancient times persons with such characteristics were regarded as an offense against nature, or as unclean and possessed of devils: The Greeks cast them into the sea, and even in later Roman times they were ordained to be flung into the Tiber. In 1474 a cock was sentenced and burned at the stake in Basel for the heinous and unnatural crime of laying an egg! In 1803, when the King Henry VII Chapel, Westminster Abbey, was restored after the neglect which it had suffered since the Dissolution of the Monasteries, over one hundred figures were found to be intact. Among them was one of Saint Wilgefort, who to avoid an unwelcome marriage prayed that she might become ugly and grew the beard with which she is shown. Her father, the king of Portugal, was so enraged that he had her crucified. Apparently the same fate befell all the sexually abnormal up to 1730. This primitive instinct of antipathy toward the abnormal or diseased can still be observed today among animals. Their presence in a herd is not tolerated; they are actively expelled or openly attacked. Achard and Thiers drew attention to a picture by Rebiera of Madeline Ventura, who, bearded at the age of 52, is shown suckling an infant. In the National Museum at Munich there is a statue in wood of the bearded Saint Madeline. At the Royal College of Surgeons there is a small book in French describing persons with characters of both sexes, accompanied by artistic representations, dated 1773. It is from mythology that one learns of transformations, both fantastic and picturesque. Sir John Bland-Sutton in his "Story of a Surgeon" stated:

> We learn from Ovid, the master of romance and vivid fancy, that Tiresias in his youth interfered with two engendering snakes, and was in consequence turned into a girl. Seven years later, he saw the same pair of snakes again copulating and separated them with a stick. He was again turned into a man, and became the most celebrated philosopher in Thebes.

From Greek mythology one learns the story of Hermaphroditus, son of Hermes and Aphrodite, who was worshipped as a divinity. He had inherited the beauty of both his parents, and thus excited the love of the nymph of the fountain of Salmacis. She tried in vain to win his affections, and one day, while he was bathing in the fountain, she embraced him, praying that she should ever be united to him. The gods granted her request, and the bodies of the youth and nymph became joined together, retaining, however, the characters of each sex.

The figures of Hermaphroditus, half man and half woman, are common in ancient art. This double sex is also attributed to Dionysus and Priapus, embodying in one being the two principles of generation and conception. Dionysus, the young and beautiful but effeminate god of wine, is described as having a manly form but one approaching the female in its softness and roundness. It is interesting to trace these changes in the attitude toward the abnormal—from veneration to persecution, so to the modern conception of toleration, for science has realized that it is only by a closer study of the abnormal that one may hope to obtain a knowledge and better understanding of those normal processes by which one lives and has one's being.

EVOLUTION OF SEX

Evolution is the great law controlling all living things; biology touches the problems of life at every point—the laws governing growth, development, actions and interactions of living things. The study of these has revealed many deep secrets of generation, and the sesame of evolution has given one fairy tales of science more enchanting than "The Arabian Nights." This has all come about by the observation of facts, by their classification and by the founding on them of general laws. The main harvests have been reaped, but the physicians of today, the gleaners and winnowers, remain to leaven the loaf.

In the highest sphere of development—the vertebrate kingdom—there are present in each sex rudiments of the accessory sexual parts of the opposite sex. There are, however, exceptions to this rule. The bodily characters and the generative cells of both sexes are combined in a few persons, and these are spoken of as true hermaphrodites. In others, the generative cells of one sex are combined with the secondary sex characters of both. Such persons, the so-called pseudohermaphrodites, are more common than the true hermaphrodites, and the anomaly is usually seen in the female. True hermaphroditism is rare in man but is more common in animals. In pigs, for example, the incidence has been estimated at 1 in every 80,000. Pseudohermaphroditism is more common in man, and in Warsaw the incidence was computed as 30 to every 800,000 of the population. Both types are more frequent in animals. Sex reversal is another feature fairly commonly observed; a hen will acquire the plumage of a cock, and instances have been reported in which a fowl has functioned as both a hen and a cock. On the other hand, a pheasant has been described with male plumage on one half of the body and female plumage on the other half. I have observed an analogous case of hemihypertrophy in a boy (aged 6½ years), on whom adrenalectomy was performed for carcinoma on the side of the hypertrophy. I have examined a dozen hens which assumed male plumage (including one duck), and in most of

these there has been a lesion (generally carcinoma) of the ovary. I have observed a cow which after failing to calve exhibited all the characters of a bull in behavior. Unfortunately, its owner was more materially than scientifically minded, and a valuable specimen was lost for research. My observations on human beings in this paper are confined to women who have acquired the secondary sex characters of the opposite sex.

SEXUAL REPRODUCTION

Science so far has been unable to explain what determines sex. Among mammals, with rare exceptions, sex once acquired is definite and unchangeable, but this stability of the sexes totters and steadily declines as one descends the evolutionary scale. In man the differentiation of the sexes has come to be regarded so much an accepted and universal feature of nature that it is necessary to discuss the questions of sexual reproduction so as to obtain some idea of the different forms in which it is manifested in nature. But in all these forms the basis of reproduction is a variant or modification of the fact that the reproductive cell, either by an inherent capacity or by the conjugation with a reproductive cell of the opposite sex, is capable of forming a new individual.

In animals and plants with separate sexes it is obvious that the two elements must always unite for each birth. In true hermaphrodites it is not obvious why they should unite; nevertheless, they either occasionally or habitually do so for the reproduction of their kind. All vertebrate animals, all insects and some other large groups of animals pair for each birth. Many hermaphroditic animals do not habitually pair. The vast majority of plants are hermaphroditic. In plant and aquatic hermaphrodites cross-fertilization can be explained by such agencies as winds and insects on the one hand and currents on the other. Apparently no land animal is capable of self-fertilization. It is a curious anomaly that in plants some species of the same family are hermaphroditic and others unisexual, yet the difference between them is very small. Hence it appears that with plants and animals intercrossing between distinct individuals is almost a universal law of nature. Hermaphroditism may occur in varying degrees in one organism. It may be demonstrable in early life (tadpole) and disappear in adult life as maleness or femaleness predominates, or it may be normal in the adult. Other animals are bisexual; they produce ova at one time and spermatozoa at another. Certain facts suggest that hermaphroditism is a primitive condition and that the unisexual condition is a secondary differentiation. Yet other facts, showing that cross-fertilization may be difficult, suggest that the bisexual condition may have arisen as a secondary adaptation.

Another, though less understood, variant in the modes of reproduction is that of parthenogenesis, in which ova produced by the female develop without being fertilized by the male. This obtains among rotifers and small crustaceans, in which in some instances the males have never been found or are absent for a season. Among bees the males may be absent for the summer or may be artificially segregated for years without affecting the rapid succession of sterile female generations and the production of drones in the beehive from eggs which have never been fertilized.

Reproduction in the elementary forms of life is by simple cell division. Thus the ameba splits to form two complete individuals. For all its simplicity, its analogy is seen in the highest forms of reproduction, the same division of the fertilized ovum into two cells, each of which may ultimately develop into separate individuals—the so-called uniovular twins. In the metazoa the same primitive form of asexual reproduction obtains. In sponges, groups or clumps of cells sequester off to form new individuals, and if a sponge is cut into pieces these may regenerate the whole. In the higher forms of life this attribute of regeneration remains the sole legacy of the reproductive cells. Volvox, on the borderline between the protozoa and the metazoa, presents several peculiar biologic phenomena. The adults are balls of cells. In such a ball reproductive units are sent adrift and divide to form new individuals. At other times some of the cells develop into ova and others into spermatozoa. The large cells are fertilized by the small. There may be volvox balls in which only ova are being made and others with only spermatozoa. Here is an organism illustrating the differentiation between somatic and reproductive cells and occurring in asexual, hermaphroditic and unisexual phases. The analogy between the higher and the lower forms of life can be pushed even further. In the protozoa, processes corresponding to fertilization are of general occurrence. Periodically, conjugation takes place in which two individuals unite temporarily or permanently. This is an incipient sexual process—the fertilization of an ovum by a spermatozoon.

SEX CHARACTERS

Only when one set of sex glands (ovary or testis) predominates is it possible to determine the sex of the individual. These are called the primary sex characters. Associated with this predominance is the development of the correlated sex organs, and sexual maturity is declared by the acquisition of secondary sex characters, which are liable to much variation. When the sex glands are completely absent or experimentally removed, as in castration, the secondary sex characters shift toward the neuter or intersex type and not to the opposite sex.

The alternation of maleness and femaleness in the same individual occurs both naturally and experimentally. Sir John Bland-Sutton gave a most vivid description of this sex reversal in the Mexican swordtail:

> It is a pretty fish, almost transparent and about three inches long. In swordtails the sexes are distinct. In the male the anal fin is represented as a pair of claspers, and the lower part of the tail is elongated, and in shape like a sword. The female has a tail of the usual shape among carp—she produces viviparously. It happens not infrequently that after producing fry two or three times, she changes her sex completely. The anal fin becomes claspers, and the lower part of the tail elongates into a sword, as in the male. Indeed the female becomes male, not only in the assumption of male livery, but sheds milt. The change is correlated with the acquisition of functional testes.

Similar changes of sex have been described in fowls.

Another curious biologic phenomenon is presented by the so-called freemartin, the female twins of cattle, which not uncommonly exhibit sex abnormalities. They are sterile and resemble castrated cattle and their internal genitalia are undeveloped. In twins of different sexes the female is usually abnormal. It has been found that there exist connecting blood vessels between the fetuses and a fusion of the chorions. It has been suggested that the female undergoes masculation under the influence of androgen entering the blood of the female. When no such fusion of blood vessels obtains, the female is normal.

SECONDARY SEX CHARACTERS

The variety and intensity of secondary sex characters has been one of the most conspicuous features in evolution. The male animal differs from the female primarily in his increased power of locomotion, his special prehensile organs, his greater size, strength endurance and pugnacity and his special weapons of offense and defense; among birds, the male differs from the female by his gorgeous plumage and decorative ornaments, his engaging antics and his enchanting song. The females are naturally endowed with organs of nourishment and protection for the young. Darwin attributed the greater decorativeness of the males to the sexual selection exerted by the females. The handsomest and most vigorous males succeed in their courtship better than their rivals and are more successful in begetting a large number of offspring.

The theory of sexual selection is dependent on the laws of inheritance and on the transmission and development of characters. The equal transmission of characters to both sexes is the commonest form of inheritance. But characters are commonly transferred to that sex in which they first appear. Secondary sex characters are transmitted by both sexes, though developed in one. Occasionally characters proper to

the male appear in the female, when she grows old or becomes diseased, for example, in the common hen. The first development of characters in the female and transference to the male is less commonly observed. Reversion of characters, which may have been transmitted through two or three generations or many generations, may appear under certain unknown favorable circumstances.

It is not known why certain characters should be inherited by both sexes and other characters by one sex alone, namely, by that sex in which the character first appeared; but it seems in a general way that variations which originate late in life tend to be developed in the same sex alone while variations which first appear early in life in either sex tend to develop in both sexes. In a few cases it must be assumed that there is an embryonic difference in the sexes to account for some characters which are seen only in one sex. For instance, hemophilia is transmitted from the parent male through the daughters, who remain unaffected, to their sons. The same obtains in some forms of color blindness. It is probable that the parent transmits characters of the asexual type which are capable of reacting to the male and the female influence of a given species.

Hair, which may be considered a secondary sex character, holds an anomalous position. It seems probable that man is descended from some hairy progenitor, yet the loss of hair must have been an inconvenience to primitive man. The commencement of denudation is seen on the under-surface of the female anthropoid ape. As women are less hairy than men, females apparently first had their bodies denuded of hair, possibly as a sexual attraction, and transmitted this character equally to both sexes. On the other hand, the male apelike progenitors of man acquired beards as a sexual ornament and transmitted them to their male offspring.[1]

HISTORY OF THE ADRENOGENITAL SYNDROME

As long ago as 1756, W. Cook established the association of hypertrichosis and adiposity with tumor of the adrenal gland. The association of secondary sex changes with tumor of the adrenal gland was known to John Hunter, and though cases were sporadically recorded, they were unsatisfactory owing to a lack of detailed pathologic investigation. It was not until 1905 that the subject was brought into prominence, in a publication by Bullock and Sequeira[2] in which eleven cases were

1. Broster, L. R.: A Review of Sex Characters, with Special Reference to the Adrenal Cortex, Brit. M. J. **1**:743-748 (May 2) 1931.

2. Bullock, W., and Sequeira, J. A.: On the Relation of the Suprarenal Capsules to the Sexual Organs, Tr. Path. Soc. London **56**:189, 1905.

reported, all in children under the age of 15 years. There were also records of cases of tumor, both benign and malignant, in a few of which the growth had been removed surgically, but the association of tumor with cortical hyperplasia was confined to postmortem observations. But apart from such generalizations, there was no indication as to how the adrenal cortex or its precise pathologic structure was implicated as a causal factor. All physicians are familiar with the varities of tumor of the adrenal gland; the tumors are spoken of generally as hypernephromas and are similar in origin, outward appearance and microscopic texture. But why only a minority are associated with virilism while the majority are not remained an enigma. This was briefly the state of knowledge when the present investigations were started.

HISTORY OF PRESENT RESEARCH

In 1927 I was asked by my colleague Dr. Gordon Holmes to remove an adrenal gland from one of his patients, a young girl with virilism, from New Zealand. By 1930, with the cooperation of Dr. Harold Gardiner-Hill, we were able to publish in the *British Journal of Surgery*[3] a paper in which our clinical material was sifted and classified into satisfactory groups. We were assisted in the histologic observations by Dr. J. G. Greenfield. By 1933 my colleague Dr. H. W. C. Vines was able to undertake a more detailed study of my pathologic material, and published a short monograph,[4] which presented a decided advance in knowledge in that Dr. Vines had been successful in finding a differential stain (the ponceau fuchsin stain) which when applied to the adrenal gland of any patient with virilism who was subjected to unilateral adrenalectomy gave a positive reaction but when used on the adrenal gland of a normal control gave a negative reaction.

THE ADRENOGENITAL SYNDROME

The adrenogenital syndrome may be defined as that condition in which secondary male sex characters appear in the female. It is associated with a retrogression of the primary and secondary feminine sex characters and their functions. The clinical picture is determined by the type of lesion and the age of the patient. Hyperplasia, owing to its slow growth, is not likely to produce such rapid changes in the

3. Broster, L. R.; Gardiner-Hill, H., and Greenfield, J. G.: The Adreno-Genital Syndrome Associated with Cortical Hyperplasia: The Results of Unilateral Adrenalectomy, Brit. J. Surg. **19**:557-570 (April) 1932.

4. Broster, L. R., and Vines, H. W. C.: The Adrenal Cortex: A Surgical and Pathological Study, London, H. K. Lewis & Co., Ltd., 1933. Broster, L. R.: The Adreno-Genital Syndrome, Lancet **1**:830 (April 21) 1934.

sexual sphere as a malignant tumor, which is usually rapidly fatal, while the course of a benign adenoma is intermediate between the two. The age of the person when the adrenal condition develops also plays an important part. As can be readily understood, the effects of the lesion will vary according to whether the organism is immature or fully developed at the time of onset.

Symptomatology.—The features of the adrenogenital syndrome are presented in the following outline:

1. The appearance in the female of hair according to the male pattern and distribution.

Fig. 1 (case 2).—Photograph of a patient with adrenal pseudohermaphroditism, showing a muscular masculine build, absence of breasts and a male distribution of pubic hair.

2. Alterations in bodily contour toward the male sphere:
   (*a*) Overgrowth of skeletal structures such as muscle and bone, lessening of the subcutaneous fat and coarsening in the texture of the skin.
   (*b*) Broadening of the shoulders relative to the pelvic girdle.
   (*c*) Enlargement of the clitoris.
   (*d*) Deepening of the voice.
3. Immature development of the female genitalia, both external and internal, and degeneration of the ovaries, giving rise to amenorrhea, either primary or secondary, or to disturbances of menstruation. There may be absence or underdevelopment of the breasts.
4. Psychologic abnormalities.

Hypertrichosis.—Male hair in the female varies in texture and distribution. It ranges from the curly crisp variety to the soft downy type, which is patchy. On the face it may take the form of a beard and mustache or that of "mutton chop" whiskers. On the trunk the hairs extend triangularly to the umbilicus from the pubis; they may cover the midsternal or lumbosacral region and the shoulders or form a halo round the nipples. The perineum and axillae are more densely covered. On the limbs they grow thickest over the thighs or on the legs and forearms, and the male mimicry may be complete to tufts of hair on the dorsa of the feet or on the proximal phalanges. In older women apical baldness and temporal recession may be conspicuous.

Changes in Bodily Contour.—The bodily contour varies with the time of onset and the degree of virilism. Persons in whom virilism

Fig. 2 (case 2).—Photograph of the same patient pictured in figure 1, showing a beard and mustache.

develops early are more masculine in appearance than an underdeveloped boy. They are short, thick set, broad shouldered, deep chested and narrow hipped, and the muscles of their limbs stand out prominently under a layer of coarse skin with little subcutaneous fat. When feminine growth has been established, no such marked alteration can take place, but there is usually some indication of variation, such as a lessened disproportion between the relative breadths of the pectoral and pelvic girdles, a tendency to "heftiness" and an undue hint of prominence of the superciliary ridge or the jaw, which is especially noted roentgenographically.

The breasts tend to be underdeveloped. There may be complete absence of both breasts; some never develop fully and others mature and then retrogress; when large, they are composed of much fatty tissue. Microscopic section of some breast tissue removed for an adenoma

in a case of virilism showed those involutionary changes which occur later in life.

In a few cases there has been some enlargement of the larynx, but in a larger porportion the pitch of the voice is altered, being deeper in tone and rough or husky. This may not be apparent in normal speech, but in moments of excitement or animation its true quality is revealed.

Changes in the Female Genitalia.—The main changes are enlargement of the male elements, with diminution of the feminine ones. The clitoris is invariably enlarged and may possess a definite glans and prepuce. When this is marked, its under-surface is grooved, as in hypospadias, but the urethra is in its normal position at the top of a small and undeveloped vagina. The mons veneris and the labia are small

Fig. 3 (case 2).—The external genitalia, with an enlarged clitoris with a glans, of the patient shown in figure 1.

and undeveloped. Laparotomy has revealed constant changes in the ovaries and a diminution in the size of the fundus of the uterus and cervix. The ovaries have been degenerate. They have been enlarged up to the size of a golf ball and pale, fibrotic and studded with small cysts, or, more rarely, they have been small and fibrotic and even calcareous. The fundus of the uterus has been as small as a thumb-nail and the cervix diminutive.

Amenorrhea may be primary—i. e., the menses never appear—or, more commonly, secondary. In the latter case menstruation starts normally and proceeds regularly, but usually either at the time of or soon after the appearance of hirsutism it becomes irregular, the intervals lengthen and the flow becomes shorter in duration, with less loss, until it finally ceases, or there may be long intervals of amenorrhea.

Changes in Psychologic Outlook.—There is a fairly high percentage of nervous and mental illness among these patients, and a great deal of it can be traced in their family histories. Briefly, they are normally heterosexual, homosexual or narcissistic, or they may present a combination of any of these three manifestations. They are pitiably conscious of their disabilities and in their silent suffering reveal the saddest aspect of human emotions.

CLASSIFICATION OF THE ADRENOGENITAL SYNDROME

The following classification was suggested from our series of cases in which unilateral adrenalectomy was performed:[3]

1. Adrenal pseudohermaphroditism.
2. Adrenal virilism.
3. Achard-Thiers syndrome, probably allied to Cushing's syndrome.

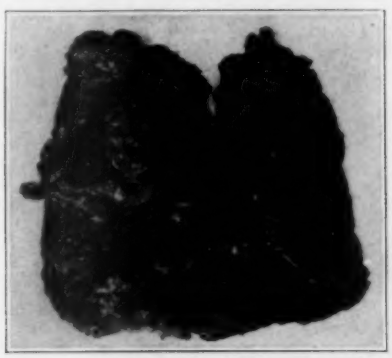

Fig. 4 (case 2).—The largest adrenal gland removed in this series of cases. The gland gave a strong fuchsinophilic reaction.

4. Postmenopausal virilism—the latest variety, associated with hypertrichosis, apical baldness, enlargement of the clitoris and a tendency toward obesity.

GROUP 1.—*Adrenal Pseudohermaphroditism.*—This is the most complete form of the syndrome. The changes occur before the bodily form and sex organs have become differentiated, and there are marked virilism, hypertrichosis of the male type, primary amenorrhea and an absence of normal feminine development.

GROUP 2.—*Adrenal Virilism.*—A later variety, in which the adrenal changes set in after puberty, is associated with alterations in the bodily form and in the external sex organs, hypertrichosis of the male type and a disturbance of sex functions. Owing to the later development of the lesion of the adrenal gland, the normal bodily changes of puberty and a period of normal menstruation are followed by regressive changes in both spheres, bodily changes toward masculinity, a diminution in

the size of the breasts and a diminution in the menstrual flow. There are in this group a relatively large number of cases, if those in which mild hypertrichosis with or without slight changes in the menstrual rhythm are included. Some of them might be described as instances of familial hirsutism. My co-workers and I have investigated other cases but have not considered the clinical condition severe enough to warrant adrenalectomy, or we have found on laparotomy no marked disproportion in the size of the adrenal glands, so that we could not expect any marked improvement by the removal of one.

Fig. 5 (case 3).—Photograph of a patient with Cushing's syndrome.

GROUP 3.—*The Achard-Thiers Syndrome.*—In this group the lesion of the adrenal gland appears to be one element in a multiglandular syndrome. The patient presents the symptom complex described by Achard and Thiers [5] as "diabetes of bearded women," a condition found at autopsy to consist of hyperplasia of the adrenal gland associated with changes in the other ductless glands. The chief symptoms are hypertrichosis on the face of the male type, obesity, glycosuria with a decrease in the tolerance to carbohydrates, hypertension and usually amenorrhea, but without other signs of virilism.

5. Achard, C., and Thiers, J.: La virilisme pilaire et son association à l'insuffisance glycolitique (diabète des femmes à barbe), Bull. Acad. de méd., Paris **86**:51, 1921.

The onset of the main symptoms in these groups may be summarized as follows:

Average age of patients	20 years
Average age of onset of menstruation	14 years
Average age of onset of virilism	15 years
Average age of increase of weight	16 years
Average age of menstrual irregularity	18–20 years

Here the onset of virilism is followed by a period of endocrine imbalance, as shown by the increase in weight. In group 2 this is temporary, whereas in group 3 it becomes permanent. The conditions of group 3 are difficult to determine. We have investigated several cases, performed laparotomy in a few and removed the adrenal gland in a case considered now to be one of Cushing's syndrome in which uni-

Fig. 6 (case 6).—The smallest adrenal gland removed in the series of cases. The gland gave the most marked fuchsinophilic reaction of all of those removed.

lateral adrenalectomy was not followed by much change, although the tissue gave a positive reaction to the ponceau fuchsin stain. The patients are all fat, hairy women with irregular menstruation. The manifestations vary in detail, but all the patients tend to show glycosuria, a high sugar curve, hypertension, erythrocythemia, a high color index and hypercholesteremia. The condition may begin as adrenal virilism and later exhibit many of the symptoms of Cushing's syndrome.

PREOPERATIVE INVESTIGATIONS

Laboratory investigations have given mainly negative results, but with rare material of this kind it is essential that every case should be fully investigated. In this series the calcium, phosphorus, cholesterol, urea and sugar contents of the blood, the gastric acidity, the sugar tolerance curve and the effect of insulin on the fasting patient have been investigated. The last-mentioned experiment was designed to see what

resistance these patients had to insulin. They were all within normal limits. The sugar tolerance curves in the majority of cases showed some distortion from the strictly normal response in that there was a normal elevation from the fasting stage but a slower return to normal. The insulin test was generally unsatisfactory from the point of view of drawing any conclusions, but there was a tendency for the patients to show a resistance to insulin. A routine roentgenogram of the sella turcica should be made. The pituitary fossa is invariably small. A roentgenogram should also be made after the injection of iopax. In this way it may be possible to detect a tumor of the adrenal gland,

Fig. 7 (case 5).—Photograph of a patient with adrenal virilism, showing a masculine muscular build, small breasts and a male distribution of hair on the abdomen, chest and shoulders.

either by distortion or by relative displacement of the renal pelvis on one side. In spite of this information, the only reliable method is direct palpation by means of exploratory laparotomy. The relative sizes of the adrenal glands can be estimated, a search can be made for accessory adrenal glands and any changes in the uterus and ovaries can be detected.

SURGICAL APPROACH

The transthoracic route has been used for operation in the majority of cases, gas and oxygen anesthesia being employed. This is the easiest approach, in view of the fact that the vascular pedicle of the adrenal

gland allows a slight range of upward movement and that the excursions of the diaphragm are better controlled by incision and retraction. It has the disadvantage of creating an artificial pneumothorax, with its concomitant respiratory distress and a long period of incumbency until the lung expands. Artificial pneumothorax has been induced prior to operation, but as it does not obviate the main issue it cannot be said that it affords any greater advantages. To overcome these difficulties a subdiaphragmatic route has now been attempted, by fracturing the last rib at its neck and retracting this upward with the diaphragm. This exposure is more difficult, and the delivery of an adrenal gland

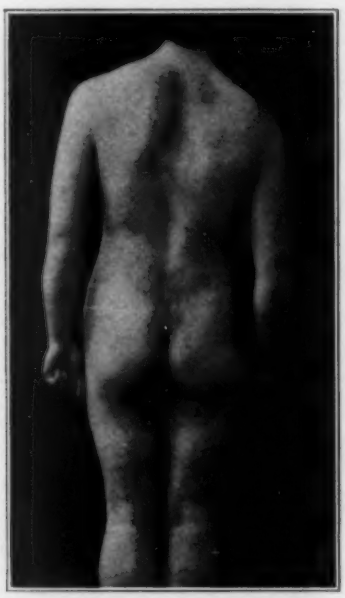

Fig. 8 (case 5).—Back view of the same patient shown in figure 7. The hair is especially thick between the shoulders, on the small of the back and on the limbs.

may be impeded by sudden diaphragmatic movements, which can be controlled only by expert anesthesia under increased pressure. On the whole, it is a decided improvement, and in our later cases the patient has been discharged within a fortnight of the operation. Inaccessibility, deep bleeding and delicate traction on a friable organ through a confined space which may spasmodically contract are the main difficulties.

OPERATIVE RESULTS

The patients submitted to unilateral adrenalectomy have shown no untoward sign so far as their general physical condition and well-being

are concerned. It is perhaps too early to speak of the ultimate value of the operation, and no hard and fast rules can as yet be laid down with regard to the selection of patients. As a generalization, it may be said that there has been a definite tendency toward the restoration of the menstrual function, and in cases in which the condition is obstinate the injection of estrogen has been useful. Another striking effect within twenty-four hours after operation is that bunches of acquired hair can be pulled out with little or no pain. These hairs grow again but gradually lose their virile character and tend to become thin, attenuated and sparser. In a few cases there has been a slight change in color.

That any dramatic change can take place is not to be expected. So far, only that adrenal gland has been removed which on palpation at

Fig. 9 (case 4).—Photograph of a patient with adrenal virilism, showing "mutton-chop whiskers." The patient gave birth to a son after adrenalectomy.

laparotomy has been considered to be the larger, though both are involved. That both adrenals are involved has been pointed out by Lescher and Robb-Smith and by Geoffrey Bourne. The left adrenal gland has been removed more often than the right. It must be recalled that the other adrenal gland may hypertrophy in the same way that surgical removal or disease of one kidney causes hypertrophy of the other or removal of half the thyroid may be followed by an enlargement of the other lobe. The largest adrenal gland measured 7.5 by 7.5 cm., and one of the smallest was 4 by 2.1 by 1.5 cm., with a weight of 3.3 Gm. (normal weight, 4.7 Gm.). The latter gland was within the limits of normal, but it gave the most intensely positive fuchsinophilic reaction. These findings suggest that virilism does not necessarily

depend on hypertrophy alone but may be associated with an apparently normal adrenal gland.

Encouraging results have been obtained only in cases of postpubertal virilism (group 2). In cases of prepubertal virilism (group 1) they

Fig. 10 (case 13).—Flat-chested, slender type of patient with adrenal virilism.

have been disappointing, but this is to be expected, for an operation performed during the second decade is too late for a condition which manifests itself only at puberty and has been present for a considerable time. At present there is no method of determining adrenal dysfunction before puberty. If this were possible, the results of earlier operations would be equally good. Time must of necessity be the final judge of

a speculative surgical procedure. A condition of slow or late development can be expected to retrogress slowly when only part of its cause has been removed.

PSYCHOLOGIC RESULTS

It must not be supposed that every woman with virilism has psychologic changes or abnormalities. When the sexuality is normal, it is normal after operation. On the other hand, we have seen abnormal

Fig. 11 (case 11).—Masculine type of patient with adrenal virilism, showing marked hirsutism.

sexuality return to normal after operation, such as changes from homosexuality to normal heterosexuality. Briefly, it may be said that operation can effect changes in personality.

"It is an error of our day that in the treatment of the human body physicians separate the soul from the body." Since these words were uttered by Socrates, physicians have separated into different sciences, but his sentiments remain the same, for it cannot be said that there has been any real rapprochement between the psychologist and the

clinician. That they have never been able to meet on common ground is perhaps understandable, because psychology is not an exact science in the same sense as the other natural sciences. The psychology of sex looms large in the teachings and writings of the psychologists, but it has received scant attention from the clinician. The latter knows little of the complex chemical interactions taking place within the cells and tissues of the human body, but with increasing knowledge dare one not hope that some of the simple and basic problems of normal and perverted sex psychology may be explained in part by organic means? Our observations in this work have encouraged us in this hope, and future research may profit greatly by a cordial cooperation between these sciences.

Fig. 12 (case 19).—Photograph of a patient with adrenal virilism with a masculine type of face.

DIFFERENTIAL DIAGNOSIS

In dealing with the question of differential diagnosis, I feel obliged, at the expense of confusing the issue, to report several recent cases in which the pathologic diagnosis has been proved. This is done in order to stress the clinical and pathologic aspects. By this means one may gain a wider outlook, by being able to visualize the controlling mechanism and the developmental processes involved in the production of sex characters.

Arrhenoblastoma.—The first case is one of clinical virilism associated with an arrhenoblastoma of the ovary (verified by Professor Schockaert, of Louvain [6]).

6. Schockaert, J. A.: L'arrhénoblastome: Notes cliniques et physiopathologiques, Louvain, Imprimerie, Nova et Vetera, 1936.

A woman aged 26, who was contemplating marriage, complained that her periods became irregular at the age of 19 and ceased at 21. At the same time hair began to grow according to the male distribution. The breasts began to recede, the subcutaneous fat began to disappear, the voice changed and the patient became morose and no longer felt attracted by men. After removal of an ovarian tumor, she began to lose her hair, her periods recommenced, her depression ceased and she began to feel like a normal woman again. Dr. Vines examined a section of the tumor but could not obtain a positive reaction to the fuchsin stain. However, if one considers the ovary to be essentially a bisexual organ, in which the medulla is of testicular origin,[7] it is not difficult to envisage such a change in sex characters which are normally under control of the gonad. There is no definite proof of this view. On the other hand, an arrhenoblastoma may be regarded as a definite testicular implant in the ovary (Vines).

Fig. 13 (case 20).—Photograph of a patient with adrenal virilism with a marked beard.

Tumor of the Hypothalamus.—The most recent case (which I was privileged to see clinically) in a series of five verified cases of virilism in the male due to hypothalamic tumor was described by Le Marquand and Russell.[8]

The patient died of rheumatic fever at the age of 5 years. At the age of 3 months he suffered from vomiting; at 14 months pubic hair began to grow, and

7. Woollard, H. H., and others: Discussion on Suprarenal and Pituitary Tumor and Their Correlation with Experimental Findings, Proc. Roy. Soc. Med. **27**:271-282 (Jan.) 1934.

8. Le Marquand, H. S., and Russell, Dorothy S.: A Case of Pubertas Praecox (Macrogenitosomia Praecox) in a Boy Associated with a Tumour in the Floor of the Third Ventricle, Roy. Berkshire Hosp. Rep., 1934-1935, pp. 31-62.

this was followed by abnormal development of his sexual organs and rapid bodily growth. His mental development corresponded with his age, but psychologically, although normally heterosexual, he was precocious in that he made obvious sexual advances to adult women. At autopsy a small tumor was found attached to the right corpus mamillare and the tuber cinereum. The adrenal gland gave a negative reaction to the fuchsin stain.

Dott and Cappell [9] observed the first well defined case of pubertas praecox associated with a hypothalamic lesion in the female

A girl, who died at the age of 8½ years from scarlet fever, suffered from fits soon after birth. At the age of 6 months she began to menstruate; at 9 months her breasts enlarged, and at 12 months hair developed. The child increased rapidly in stature for four and a half years. Mentally she showed a precocity for remembering tunes, and psychologically she was homosexual, preferring the

Fig. 14 (case 21).—Photograph of a patient with adrenal virilism with a goatee variety of beard.

company of adult women. From the age of 4½ onward, she showed a definite physical and mental progeria. At autopsy, Professor Cappell, of Dundee, verified and localized a benign astrocytoma arising from the neighborhood of the mamillary bodies and involving the posterior half of the floor of the third ventricle. The tuber cinereum was pushed slightly forward but was not actually involved. The tumor bulged into the third ventricle and filled the interpeduncular space.

The condition in this case is therefore the direct counterpart of that occurring in males and is most interesting in view of the fact that the only other tumor in this region which causes sex precocity—a tumor of the pineal body—has been recorded only in boys.

Cushing's Syndrome.—The association of Cushing's syndrome with a basophil adenoma of the pituitary gland is so well known that it

9. Dott, N. McO., and Cappell, D. F.: Personal communication to the author.

facilitates any discussion on the subject. I have already drawn attention on clinical grounds to a large group of cases in which many of the primary and intermediate symptoms of this syndrome are presented, and with a multiglandular condition of this sort it is to be expected that there would be a similar variation in the pathologic process. To prove that this is so, I wish to draw attention to the following facts which have come to my attention.

(*a*) Two cases of the Cushing type associated with carcinoma of the adrenal gland and a cyst of the pituitary body.

1. A woman aged 33 had increasing hirsutism, obesity and amenorrhea, frequent headaches, vomiting and baldness. A carcinoma of the

Fig. 15 (case 22).—Photograph of a patient with adrenal virilism with a mustache.

adrenal gland was found, the gland being four times the normal size. It gave a weakly positive reaction to the fuchsin stain. A cyst was found in the pituitary body.[10]

2. A woman aged 51, who was married at 39, after the birth of the youngest child had amenorrhea, hirsutism, baldness, deepening of the voice, an increase in weight, headache and failing vision. The blood pressure was 186 systolic and 116 diastolic. An adenocarcinoma of the right adrenal gland was found, with a secondary metastasis in the lung and a cyst in the pituitary body.[11]

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10. Hare, D. C.: Two Cases of Dyspituitarism, Proc. Roy. Soc. Med. **27**: 1017-1020 (June) 1934.

11. Unpublished data. Personal communication between H. W. C. Vines and Professor Webb.

(*b*) In two cases virilism clinically indistinguishable from Cushing's syndrome was found to be due to tumor of the adrenal gland (Lescher and Robb-Smith [12] and Hare, Ross and Crooke [13]). In one of these the fuchsin stain elicited a positive reaction not only in the tumor but in the opposite adrenal gland. In one case there was a slight increase in the basophil cells of the pituitary body.

(*c*) Data on five cases of proved basophilism of the pituitary gland have been collected at the Charing Cross Hospital. In each of the cases the adrenal glands gave a negative reaction to the ponceau fuchsin stain, and in no case were there any of the clinical signs associated with virilism or with Cushing's syndrome. In a sixth case of mild virilism associated

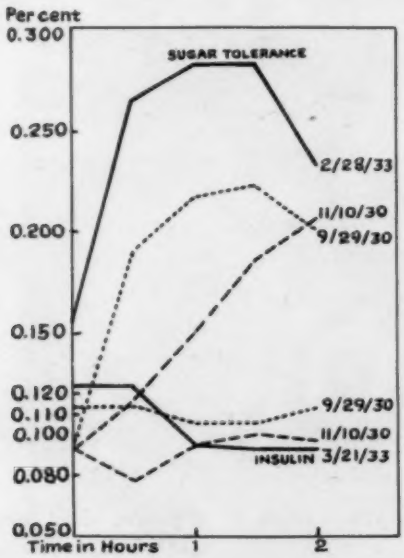

Fig. 16 (case 3).—Sugar tolerance curves made after removal of the right adrenal gland and one curve made after the administration of insulin.

with narcissism the patient died of a pulmonary embolus after appendectomy, and we found a well marked nodular basophilism of the pituitary gland. The adrenal glands gave a negative reaction to the ponceau fuchsin stain.

(*d*) One case is of particular interest in that Vines discovered a small meningioma, the size of a pea, situated at the attachment of the

12. Lescher, F. Graham, and Robb-Smith, A. H. T.: A Comparison of the Pituitary Basophilic Syndrome and the Adrenal Cortico-Genital Syndrome, Quart. J. Med. **4**:23-35 (Jan.) 1935.

13. Hare, D. C.; Ross, J. M., and Crooke, A. C.: Cortical Carcinoma of the Suprarenal with Cushing's Basophil Pituitary Syndrome, Lancet **2**:118-122 (July 20) 1935.

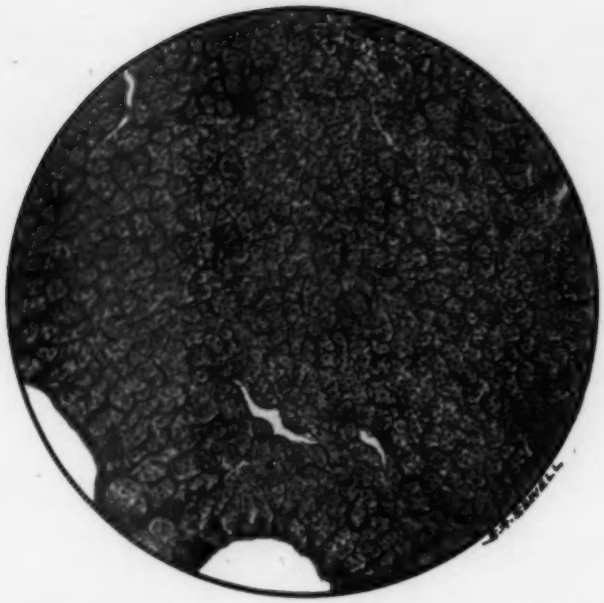

Fig. 17.—Photomicrograph of the adrenal cortex in a case of virilism. The fuchsinophilic reaction was positive.

Fig. 18.—Photomicrograph of a normal adrenal gland removed from a woman at nephrectomy. The fuchsinophilic reaction was negative.

Fig. 19.—Photomicrograph of the adrenal cortex of a 16 week male fetus. The fuchsinophilic reaction was positive.

Fig. 20.—Photomicrograph of the adrenal cortex of a 15 week female fetus. The fuchsinophilic reaction was negative.

stalk of the pituitary body to the hypothalamus. The patient was a slim young woman of 23, who died of chronic nephritis. She had a masculine body with fairly marked hypertrichosis; the adrenal glands were normal and the ovaries were cystic. There was no obvious evidence of an endocrine disturbance, and the only effects were those of hypothalamic pressure.

APPLIED HISTOLOGY (PONCEAU FUCHSIN STAIN)

With this range of clinical material it was possible to argue that if no irregularity was found in the arrangement or shape of the cortical cells there might possibly be a difference in their function. By using the ponceau fuchsin stain, Dr. Vines was able to show that in our series of cases of virilism in which unilateral adrenalectomy was performed the cytoplasm of the cells of the cortex contained a vivid red granular material, mainly in the inner and the middle zone. The color varied in intensity and was most vivid in an adrenal gland which was within the normal limits of size, suggesting that the response was as much qualitative as it was quantitative in the case of hyperplasia.

To exclude the possibility of postmortem changes taking place in the adrenal gland, a control series was started by removing portions of normal gland in the course of routine operations on the kidneys. These all gave negative reactions to the stain, as did all normal adrenal glands studied post mortem. A collection of several autopsy specimens of tumor of the adrenal gland associated with virilism gave a positive reaction, showing that the fuchsinophilic material in the cells is capable of surviving postmortem conditions. It seemed unlikely that some isolated reaction had been obtained in the adult; so a further search was made into fetal adrenal glands. Dr. Vines found a strong fuchsinophilic reaction in the male fetus between the ninth and the seventeenth week. In the female fetus the reaction was not so strong and of shorter duration, lasting from the eleventh to the fourteenth week. After the twentieth week it was absent in both sexes. This observation may well prove to be one of fundamental importance in the elucidation of many difficulties. It establishes an early and passing phase in embryology, common to both sexes, but less marked and of shorter duration in the female.

In other tissues of the body traces of this reaction were found in the interstitial cells of the testis, the corpus luteum and the anterior lobe of the pituitary gland.

Our clinical evidence and operative results have established this differential staining reaction with the condition of maleness in the female, and this has naturally suggested the possibility that "the substance so staining must be closely related to or even identical with the

male hormone or its precursor"[14] and that its presence in the intercellular spaces further suggested that it acted by way of the blood stream. We have already drawn attention to the tendency toward hypercholesteremia, and the adrenal gland has long been credited with the regulation of the sterol metabolism. Furthermore, the presence of this stain is associated with a benign growth of tissue in bone, muscle, fat and skin alien to its normal host. Doubt has been cast by Bourne[15] on our interpretation of the fuchsin stain, and he expressed the opinion that it may be due to mitochondrial changes occurring in the cortical cells. In an ingenious theory he links up this subject with the work of Dodds, who showed that the androgenic and estrogenic substances are derivatives of the sterols and are chemically linked to the coal tar substances of carcinogenic activity. He also stated that carcinogenic principles may be discovered in the interaction between the cortical cells and the sterol metabolism.

COMPARATIVE ANATOMY OF THE ADRENAL GLAND

In order to obtain a clear conception of the background of our work, it is necessary to refer briefly to the comparative anatomy of the adrenal gland and to trace the steps which have led to the formation of this highly specialized organ.

In its primitive form the cortex is separate and intimately connected with the reproductive system. It then becomes associated with the cells of quite a different system, the sympathetic, which ultimately forms the medulla. It appears first in fish and increases in importance so that the glands become essential to life in the high animals. In sharks and rays the two cell systems are separate. The cortex is known as the interrenal body and is associated with a marked development of the sexual system. In amphibians (frogs) the two cell systems make a definite advance toward each other and are arranged in a chain along the lumbar segments, until in reptiles and birds one finds them intimately mixed to form a solid organ. In mammals and man the medulla becomes completely enclosed within the cortex, and the method by which these sympathetic cells wander into the cortex in man has not been observed even in the higher apes. From the nature of such a migratory process it is not uncommon for cells to become detached and to form accessory adrenal glands, which may contain the elements of one or the other or of both of these cell systems. In man the adrenal glands reach the maximum size of their development at birth, when each is about one-third the size of the kidney. The inner layers of the cortex

14. Adrenal Virilism, editorial, Brit. M. J. **2**:880 (Nov. 11) 1933.

15. Bourne, Geoffrey: The Sterols, Sex Hormones, and Cancer, J. Cancer Research Com. Univ. Sydney **7**:34-39 (Aug.) 1935.

then undergo an astonishing and rapid process of absorption and regeneration, until the size of the gland is reduced to one thirtieth of that of the kidney. The glands enlarge at puberty, during pregnancy and at the menses. Between the fourth and the fifth decade they reach their zenith, and then they gradually undergo senile involution. It occasionally happens that this adult stage of the gland is present at birth and is then associated with anencephaly, so that it has been thought that the cortex is in some way connected with the development of tissues rich in lecithin.

APPLIED EMBRYOLOGY

In point of time the cells of the adrenal cortex can be recognized about the fourth week and are derived from the same mass of cells, the genital ridge, which also give rise to either the testis or the ovary. There is thus a common origin for the cortex and the sex gland. The determination of sex takes place about the seventh week, and, as has been noted, the appearance of the fuchsinophilic reaction commences from two to four weeks later.

Crew [16] stated: "That so far as is known, the sex chromosome mechanism is the sex determining mechanism, but in many cases this mechanism can be overridden and the sex of the individual determined in other ways." It is therefore reasonable to argue that a strong and prolonged male phase in the female fetus may possibly be one of those factors which modify sex. To what extent is still a matter of conjecture. A positive reaction has been found in a case of true hermaphroditism, and it is probable that sex reversal, from female to male, will come to be included in this category. But it is known that the cells of the adrenal cortex still retain the power of developing this substance into adult life and that it may become activated at certain periods of physiologic stress, such as puberty. If this explanation is accepted, it readily accounts for groups 1 and 2, which have already been considered clinically.

However, in group 3 the problem is not so simple. It may be argued that in adult virilism there is a failure on the part of some feminizing influence to counteract the male phase. The brief duration of this male phase in the female fetus suggests that it is suppressed, and this suppression is due to some mechanism dependent on the functional activity of the other endocrine organs. That there is some such mechanism was found by Dr. Vines in two female fetuses, in which a prolonged male phase was accompanied by a definite hyperplasia of the pituitary gland. Hence virilism may be due to a failure to maintain the normal restrictive action of the pituitary gland on the masculating potentialities

16. Crew, F. A. E.: Sex Determination, London, Methuen & Co., Ltd., 1933.

Summary of Data on Cases of Virilism

Group	Case	Age	Date	Degree of Virilism	Menstrual History	Outlook	Genitalia	Adrenal Removed	Fuchsin Reaction	Result
1	1	15	9/27	Marked	Primary amenorrhea	Normal	Infantile uterus	Left	Strong	Very slight change; abroad
1	2 (figs. 1, 2, 3 and 4)	22	9/28	Very marked	Primary amenorrhea	Indifferent	Infantile uterus; cystic ovaries	Left	Strong	Very slight change; complexion clear with depilation
3	3 (figs. 16 and 5)	18	10/30	Slight	Amenorrhea for 18 mo.	Childish	Infantile uterus; cystic ovaries	Right	Strong	Loss of hair; no change
2	4 (fig. 9)	21	6/29	Moderate	Amenorrhea for 10 mo.	Normal	Small uterus	Left	Strong	Good result; loss of hair; periods regular; married and had a son since operation
2	5 (figs. 7 and 8)	22	10/30	Marked	Irregular periods	Normal	Small uterus; cystic ovaries	Left	Strong	Menses regular; hair less, coming out; headaches less severe; friends remarked on improvement; more feminine
2	6 (fig. 6)	20	7/31	Moderate	Amenorrhea for 1 yr.	Normal	Small uterus; cystic ovaries	Left	Strong	Good; periods fairly regular; hair not coming out so easily as at first; more interested in life
2	7	21	2/32	Moderate	Regular periods	Normal	Infantile uterus; cystic left ovary	Right	Strong	Periods regular; happier; good; complexion clear; no hair
2	8	29	6/32	Slight	Amenorrhea for 9 mo.	Homosexual	Infantile uterus; cystic ovaries	Left	Moderate	Not much change; bedridden before and after operation; has had four periods since; died in 1936; cause unknown
2	9	20	7/32	Moderate	Irregular periods; amenorrhea at times	Normal	Infantile uterus; cystic ovaries	Right	Moderate	Hair comes out easily; periods regular; outlook improved and changed to normal; married recently
2	10	18	8/32	Moderate	Late onset; irregular periods	Indifferent	Infantile uterus; cystic ovaries	Right	Strong	Hair comes out easily; periods regular; more feminine in outlook
2	11 (fig. 11)	30	4/33	Marked	Regular periods	Normal	Small uterus; fibrous ovaries	Left	Fairly marked	Good; hair white at ends, pulls out easily; periods regular; complexion improved
2	12	35	5/33	Moderate	Amenorrhea at 26	Male tendencies	Small uterus; big cystic ovaries	Left	Strong	Amenorrhea continues; brighter outlook; much the same; fair

2	13* (fig. 10)	32	11/33	Moderate	Regular periods; ceased at 26	Homosexual	Small fibroma in uterus; small cystic ovaries	Left	Fairly marked	Period started 2 days after operation; hair all out in 2 wk.; periods normal; psychology now normal; very good result
2	14	26	8/33	Moderate	Irregular periods; ceased at 20	Homosexual	Infantile uterus; cystic ovaries	Left	Moderate	Hair coming out; periods regular; outlook brighter and more normal; very good result
4	15*	54	10/33	Slight	Hysterectomy and right ovariotomy at 38	"Disgusted" with herself; sensitive	Remaining left ovary cystic	Left	Moderate	Hair all out in 2 wk.; slight growth on head; in statu quo
2	16	28	5/32	Moderate	After 21 less and less	Indifferent; prefers men; does not like marriage	Fibroid tumor in uterus; left ovary large; both cystic	Right	Strong	Marriage difficulties; improved
2	17	19	3/34	Moderate	Period every 9 mo.	Fond of girls	Infantile uterus; large cystic ovaries	Right	Strong	Increased heterosexuality; improved
2	18	40	7/34	Slight	Period every 28 days for 3 days; scanty	Disinterested in opposite sex	Fibroid tumor in uterus; right ovary normal lutein cyst of left ovary	Left; weight 7.4 Gm.	Strong	Hair gone; periods regular
2	19 (fig. 12)	21	4/35	Marked	At 12 period irregular: amenorrhea 2-10 mo.	Normal	Small uterus; small cystic ovaries	Left; weight 4.4 Gm.	Strong	Periods normal; free from hair; heterosexuality increased
2	20 (fig. 13)	29	6/35	Moderate	Regular periods; 3-4 days every 28 days	Reserved and nervous	Small uterus; fibrous cystic ovaries	Right; weight 6.8 Gm.	Moderate	Satisfactory; face clear
2	21 (fig. 14)	29	8/35	Moderate	Irregular periods	Homosexual	Small uterus; cystic ovaries; lutein cyst	Right; weight 5 Gm.	Strong	Periods improving; less hair; no psychologic change
2	22 (fig. 15)	40	9/35	Slight	Irregular periods for 10 yr.; regular for 15 yr.	Heterosexual	Small uterus; ovaries fibrotic	Right; weight 5.8 Gm.	Strong	Periods regular; moustache clear; increased heterosexuality

* Married.

of the female adrenal gland. This type would be associated with a dysfunction of the pituitary gland, the clinical picture being determined by the predominance of one or other factor, and when this dysfunction is in the ascendancy there is a shift toward the type of basophil syndrome of the pituitary gland described by Cushing.

CLINICAL SUMMARY

From an examination of over sixty cases of virilism of varying degree, a few general conclusions may be drawn. That heredity plays a part there is no doubt. A family history of hirsutism was present in 25 per cent, and in these it was twice as common on the distaff side. On the male side it ranged from grandfather, father to brothers; on the female, from mother, sisters, aunts, daughters and nieces, being more frequent in the aunts and sisters. It thus appears to be transmitted more on the female side. There is slight evidence that it is associated with the events which occur at birth. It occurred in two cases of twin births and in one case of premature birth, and in one case it appeared in the 4 year old daughter, within three months of its onset in the mother. With regard to other endocrine disturbances, it appeared in several persons whose mothers suffered from exophthalmic goiter, and in one whose mother suffered from diabetes. In case of mild virilism there were symptoms of hyperthyroidism. One point of practical importance must be stressed, and that is that women with virilism are comparatively infertile, as one would expect from the nature of the pathologic process. If they conceive, they are apt to miscarry. On the other side, one patient on whom unilateral adrenalectomy had been performed and who suffered from amenorrhea has since married and produced a son.

CONCLUSION

A series of twenty-three cases of virilism are presented in which unilateral adrenalectomy was performed without a fatality. We have found a specific differential staining reaction in the cells of the adrenal cortex, which is absent in controls. It is also present in the tumor cells in cases of virilism due to neoplasm. This stain has been verified, and its presence shown in the opposite adrenal gland at autopsy by others. This stain is present in the fetus of both sexes, and virilism can be explained by its abnormal persistence in the female. In some of our patients we have observed an increased amount of cholesterol in the blood. We cannot say what the significance of this stain is. It is associated with definite changes in the growth and development of the body tissues, which have reverted to normal after unilateral adrenalectomy. In some cases it has been associated with alterations in the psychologic outlook of the patient, which have reverted to normal after operation.

The same changes have been observed in arrhenoblastoma of the ovary. Cases of pubertas praecox are cited to show that lesions of the hypothalamus are associated with the premature onset of puberty and may be accompanied by psychologic changes. These effects are gonadotropic, of the isosexual type, occurring in children.

This advance in knowledge is all of recent origin, and lies rooted primarily in the fertile soil of surgery. With careful observation by the clinician and close investigation by the pathologist and biochemist and by intelligent cooperation in the study of the rare and limited material, one may now hope that with wider application these tender bulbs may sprout and yield a richer harvest.

Figures 1, 2, 3, 4, 5, 7 and 8 have been published in the *British Journal of Surgery* (**19**:557-570 [April] 1934) and in "Post-Graduate Surgery" (Rodney Maingot, editor, New York, Appleton-Century Company, Inc., 1936, vol. 2). Figure 11 has been published in the *Lancet* (**1**:830 [April 21] 1934) and in "Post-Graduate Surgery," and figure 16 was redrawn from a chart which appeared in the same issue of the *Lancet*. Figures 6 and 9 have appeared in "Post-Graduate Surgery." Figures 17, 18, 19 and 20 have been published in "The Adrenal Cortex," by Broster and Vines (London, H. K. Lewis & Co., Ltd., 1933), and in "Post-Graduate Surgery."

XANTHOSARCOMA OF THE CHEEK SUCCEEDING XANTHOSARCOMA OF THE FOREARM

MULTIPLE TUMORS VERSUS METASTASIS

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While xanthosarcomas are rare, there are weightier reasons for making this report. The occurrence of two widely separated tumors was responsible for a consideration of (1) the problem of metastasis (involving the question of genuine malignancy) versus pluricentric tumors and (2) complex problems of internal medicine ranging from the embryologic, developmental aspects of tumors of the acoustic nerve to the diversified changes that may occur in tumors incidental to hypercholesteremia.

Thus, with xanthomatous tumor-like masses occurring (1) in granulation tissue (Garrett [1]), (2) in diabetic and pseudodiabetic conditions (Weidman and Schaffer [2]), (3) with adenocarcinoma of the stomach, (4) with adenocarcinoma of the duodenal papillae, (5) with strictures of the bile ducts, (6) with acute pancreatitis and (7) with hydatid cysts, the attention of the surgeon must be drawn to the field of disturbed general lipid metabolism, which most of the lesions just mentioned can connote.

In short, it is no longer sufficient to view the yellow tumor of tendons and subcutaneous parts simply in a prognostic light; it is incumbent on the physician to distinguish between the yellow color due to blood pigment and that due to lipoid which is part of a true xanthomatous change. In the case of the latter, a broad field of internal medicine opens up, inviting the cognizance of the surgeon as well as of the pathologist, internist, pediatrician, laryngologist and ophthalmologist.

It is of much less importance that the knowledge that lesions occurred on the hard palate and elsewhere in the mouth of the patient whose case I am reporting may prove useful in the differential diagnosis of oral conditions in which perhaps an obvious primary focus is lacking. Still, the proximity of tumors of the acoustic nerve (occasionally xanthomatous) to the vault of the pharynx and mouth may bring the diagnosis

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From the Laboratory of Dermatological Research, University of Pennsylvania and the Pennsylvania Hospital.

1. Garrett, C. A.: Tumors of the Xanthoma Type, Arch. Surg. **8**:890 (May) 1924.

2. Weidman, F. D., and Schaffer, H. W.: Xanthoma of the Skin and Larynx, Associated with Carcinoma of the Stomach and a Regressive Xanthoma of the Pons, Arch. Dermat. & Syph. **35**:767 (May) 1937.

of oral conditions into the realm of such important states as intracranial tumors. Indeed, such a consideration was brought up by the studies on my patient.

REPORT OF A CASE

History.—Bessie H., aged 34, a Negress, was admitted to the Pennsylvania Hospital on June 7, 1924, on account of a large tumor on the right arm. It was the size of a grapefruit, apparently extended upward from the ulna to the humerus, and was firmly fixed to the underlying parts. The radius and ulna were adherent to each other; it was scarcely possible to flex or to extend the forearm.

The mass of the tumor extended definitely above the general cutaneous level; while it was not ulcerated, the skin was excessively thin, and its surface was made up of such numerous, shallow lobulations that there was a close approach to a fungoid form. In view of the dark color of the Negress, the intrinsically yellow color of the tumor was not recognized clinically, and the xanthic phases in the case were not identified until pathologic examination.

Fig. 1.—Xanthosarcoma of the forearm.

In 1913 the patient received a blow on the right forearm; succeeding the contusion, a tumor developed slowly. In seven years it became as large as an apple; subsequently it grew more rapidly. At times neuralgic pains extended down the arm. The patient lost 35 pounds (15.9 Kg.) from 1921 to 1924.

Physical examination did not disclose evidence of metastasis, except for an exostosis of the right malar bone. The mouth was examined carefully. The roof was high, and the teeth were in fair condition; certainly there were no metastatic lesions in the mouth at that time. From the clinical examination of the chest the possibility of pulmonary tuberculosis was considered. However, roentgen examination did not confirm this suspicion.

On admission the liver and spleen were not palpable, nor were there any other palpable masses in the abdomen. The uterus was slightly enlarged, but there were no palpable masses.

Roentgenograms of the accessory nasal sinuses showed only a slight cloudiness over the right antrum. A roentgenogram of the right arm showed that the lower third of the humerus and the upper three fourths of the radius and ulna were involved; there was destruction of the bone, as well as evidence of attempted regeneration. This resulted in marked deformity, particularly of the radius and ulna. In one place the two bones were particularly deeply eroded. Practically all trace

of the medullary canal was lost. The density of the bone varied irregularly from place to place. The roentgenologist confirmed the diagnosis of sarcoma, and was of the opinion that the bone had become involved secondarily.

Clinical Summary.—Following a contusion of the forearm, a tumor developed slowly for seven years; in the succeeding four years it developed more rapidly. The large size and the evident infiltrative and destructive propensities of the lesion justified the diagnosis of sarcoma, which was confirmed roentgenologically. No metastases were apparent, but an enlargement on the malar bone was noted which subsequently proved to be xanthomatous (and probably also xanthosarcomatous).

Pathologic Examination.—Following amputation 4 inches (10.16 cm.) below the head of the humerus the specimen was dissected and the extent of the infiltration by the tumor was determined. Loose polyps of tumor tissue were found infiltrating, but not eroding, the cavity of the joint; spaces in the lower third of the forearm were also infiltrated. The muscles of the forearm and also the posterior group of muscles of the upper part of the arm were almost completely atrophied. The osseous tissue was markedly changed; the humerus was perforated, and there was a small round cavity, 2 cm. in diameter, just above the epiphysial line. The cavity showed a smooth wall lined by tumor tissue, which also extended into the medullary cavity. The radius and the ulna showed considerable absorption of bone salts. At the distal end of the humerus, tumor tissue was found infiltrating the medullary cavity.

Histologic Observations.—Ten blocks of tissue were selected from different parts of the tumor in order to gain as representative a picture as possible of the entire composition of the growth. It was desired particularly to determine the presence or absence of necrosis; hence those parts which seemed softest or hemorrhagic were selected. In no case was a focus of necrosis found in any of the blocks of tissue.

Tendons: Two sections were taken from the wrist and one from the upper part of the arm. The only abnormality consisted in an extremely slight hyperplasia of the cells lining the sheath.

Fungating Portion of the Lesion: This section consisted chiefly of whorling strands of young fibrous tissue—typical fibrosarcoma. From place to place small giant cells occurred and also xanthoma cells. This fibrosarcomatous part blended imperceptibly with the corium and even the papillae of the skin. In the deepest parts of the section the cells were extremely xanthomatous, cytoplasms being fused to produce smaller and larger areas of pink granular material in which the nuclei of the xanthoma cells still persisted. Probably 80 per cent of this large section exhibited fibrosarcomatous (no xanthoma) features, while the remainder consisted either of large, more or less polyhedral cells (swollen fibroblasts) or xanthoma cells.

Uppermost Portion of Tumor (Infiltrating): Two sections were submitted. There was a definite fibrous capsule around one section. The tumor consisted exclusively of large, more or less polyhedral cells, many of which were xanthomatous. Fibrosarcomatous characteristics were exhibited only in small and widely scattered areas, although here and there were some remnants of an original stroma of fibrous tissue. Giant cells were numerous. These characteristics were repeated in the second block of tissue selected.

Interosseous Membrane: There was only a suggestion of sarcomatous change, thus suggesting that the nuclei of fibrous tissue cells were moderately hyperplastic in some positions. The most striking feature was the extraordinarily broad and

dense accumulation of lymphoid cells around the blood vessels. Such cells did not tend to xanthomatous change, although spindle cells in their immediate proximity exhibited such a change. Plasma cells were widely infiltrated throughout the section. They did not tend to xanthic change. Skeletal muscle fibers were atrophic; their cytoplasms were rarefied and suggested xanthomatous change. Their nuclei were tremendously hyperplastic.

Fig. 2.—The postoperative specimen. Samples of tissue were taken from ten portions of the tumor to test the lipid partition of the fats: *1*, the interosseous fibrous tissue; *2*, the most central parts of the tumor; *3*, the summit of the fungus growth (superficially ulcerated); *4*, the fibrous capsule; *5*, the central portion of the tumor; *6*, areolar fat; *7*, muscle; *8* and *9*, the peripheral advancing part of the tumor, and *10*, a portion at the junction of the fibrous center and the definitely xanthomatous part.

Skin of the Wrist: Two sections were submitted. In one there were no xanthomatous features; the nests of xanthoma cells which Kreibich [3] reported in grossly normal skin of a diabetic patient with xanthoma were not repeated here. In the second section the deepest parts of the skin were heavily infiltrated by lymphoid cells, particularly the subcutaneous fat. There was definite fibrous hyperplasia in the deepest parts of the subcutaneous tissue, together with a minor formation of xanthoma cells. However, the true skin was free from xanthomatous foci, as was the first section.

Likewise, sections of normal skin from the back of the hand and the palm failed to disclose xanthomatous foci.

The Intramuscular Nodule: This was selected for study with the idea that it would represent tumor processes in their earliest stage, i. e., in the most outlying and detached portion of the entire tumor. Again dense infiltrations of lymphoid

Fig. 3.—Roentgenogram illustrating the erosion of the bones.

and plasma cells around the blood vessels were noted. Skeletal muscle fibers had lost their transverse markings and had become so disorganized as to simulate white fibrous tissue. The tumor cells were predominantly spindle shaped, and there were comparatively few xanthoma cells. The matrix of fibrous tissue between the cells was dense and abundant.

Frozen Sections: The xanthoma cells were found to contain neutral fat almost exclusively when stained by sudan III. Crystals could be recognized only from place to place, sometimes in comparatively large masses. They stained red indifferently compared with the neutral fat. With polarized light only a portion of the crystals was found to be doubly refractive. A source of error consisted in the presence of certain globules of neutral fat which lay in a plane immediately

3. Kreibich, C.: Zosteriform Xanthoma, Arch. f. Dermat. u. Syph. **152**:365 (Dec. 3) 1926.

above the doubly refractive crystals; under these circumstances such crystals appeared to be red. The error was eliminated photographically by the use of a blue screen, which gave a truer quantitative photographic registration of the doubly refracting substance by blocking out the "contaminating" red (neutral fat) factor.

Summary and Comment.—The more peripheral, presumably advancing parts of the tumor showed characteristics of fibrosarcoma; the xanthomatous changes appeared in the older, more central regions. As

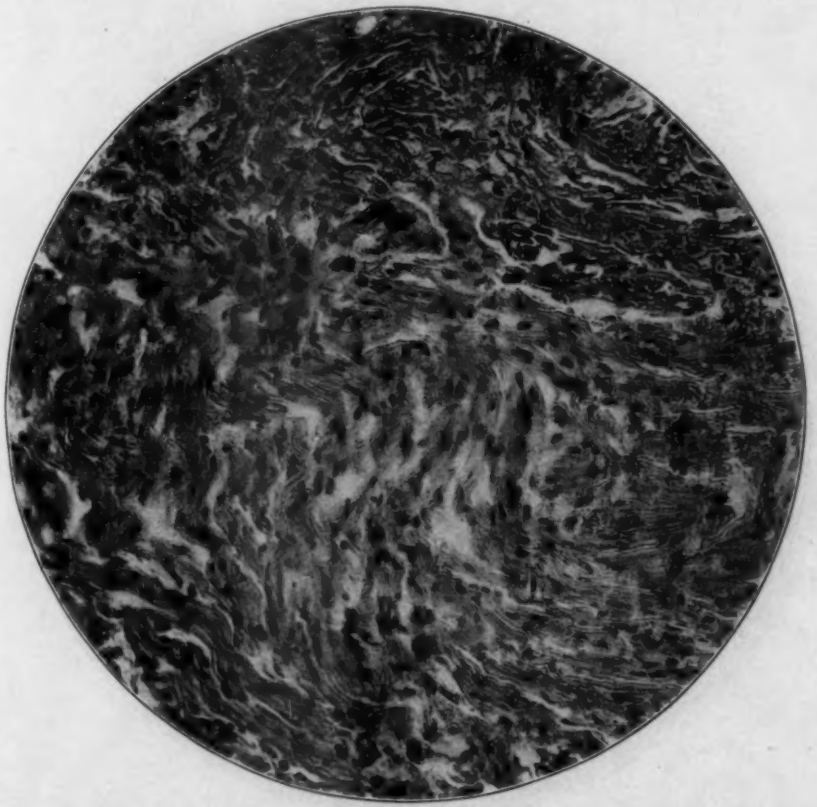

Fig. 4.—Xanthosarcoma of the forearm: the fibrous portion, showing evidence of the fundamentally fibrous nature of the tumor.

transitions from spindle and polygonal cells into xanthomatous cells could be traced (best in the peripheral position), it appeared that the tumor was essentially a fibrosarcoma and that the xanthomatous changes had been superadded. The lipids concerned appeared to be overwhelmingly neutral fats; it was assumed that the doubly refractive ones represented cholesterol. Incidentally, the latter type of lipids tended to occur in masses. Since they were not recognizable in individual cells, it was assumed that they occurred not as part of the essential metabolism of

the xanthoma cell but as a secondary development. However, I have no idea what processes are involved in this secondary development.

SECOND OBSERVATION OF THE PATIENT

The patient was discharged with a completely healed wound three weeks after operation. Five months later she was readmitted to the hospital on account of swelling on the right side of the face and deafness. At three places, i. e., over the

Fig. 5.—Xanthosarcoma of the forearm: the fibrous portion, showing early lipoid change (many minute vacuoles).

right maxilla, in the region of the upper antrum and posterior to the right ear, there were four sessile growths, varying from 3 mm. to 8 cm. in diameter. Except for the lesion first mentioned, they were adherent to the overlying skin, which was hyperpigmented, thus preventing recognition of any yellow color.

However, a yellowish brown color was noted in the nodules in the mouth. These were most numerous over the upper right alveolar ridge; in particular, a polypoid extension protruded outward from the interval once occupied by a molar tooth, and attracted attention to this location as a likely center for the entire

process. Furthermore, there appeared to be a definite fulness of the immediately underlying parts. The nodules were movable, hard and of irregular size and shape. Some were discrete, while others were confluent, forming larger masses.

The nose did not appear to be involved. The air passages seemed to be free; there was no discharge, and the mucous membranes appeared normal. The external auditory canals were clear. There were no gross ocular symptoms, such as exophthalmos, palsy or ptosis. No softenings or thickenings could be detected on the cranium; it was of normal shape and circumference.

Fig. 6.—Beginning transformation of spindle cells, in the bundle immediately above the equator, into xanthoma cells just below.

The mass over the right maxilla was not adherent to the skin but was definitely incorporated with the maxilla. In the buccal wall immediately subjacent, a hard mass could be shifted about with ease; it measured 1.5 by 0.75 by 0.50 cm. It appeared from this fact that the mass occupied the antrum and adjacent tissues, even as far as the cutaneous and oral mucosa.

No nodules were visible on the vaginal and cervical mucosa.

Physical Examination.—Skin: The patient stated that subsequent to the operation certain old scars became elevated and itchy. One such scar, on the right side of the chest anteriorly, was definitely lemon yellow and elevated. (A specimen

was removed for biopsy; while the lesion had not resembled keloid clinically, the pathologist reported only a subcutaneous fibrosis, with no foam cells or other lipoid deposition.)

Abdomen: There was now fulness in the flank owing to a questionable small amount of ascites (not present at the first admission), and the liver was palpable; no bosses were felt on the surface. Otherwise no abnormalities were detected.

Eyes: No crystals (referable, for instance, to deposits of cholesterol) were recognizable. The internal examination gave normal findings.

Fig. 7.—Xanthosarcoma: section illustrating the close relationship between fibrous tissue and the xanthoma cells.

Laboratory Examinations.—The cholesterol of the blood measured 177 mg. per hundred cubic centimeters; the sugar, 90 mg.; the urea nitrogen, 68 mg., and the uric acid, 3 mg.

Examination of the urine failed to reveal anything abnormal. The Wassermann test of the blood gave negative results with both cholesterolized and noncholesterolized antigens. The blood count revealed: hemoglobin, 58 per cent; red blood cells, 3,080,000; white blood cells, 5,200, and a differential count of 59 polymorphonuclears, 40 lymphocytes and 1 basophil.

Roentgen Examination.—Stereoscopic roentgenograms of the accessory nasal sinuses, taken both laterally and anteroposteriorly, did not give evidence to substantiate the diagnosis of xanthosarcoma.

The consulting otolaryngologist found extensive infiltration around the right side of the fauces, probably causing occlusion of the eustachian tube. The mucous membranes of the tympanum were markedly retracted as a result of the occlusion of the eustachian tube, accounting for the deafness.

Course.—The patient was given a diet poor in cholesterol for several days. The cholesterol value of the blood after two days of this regimen was 132 mg. per hundred cubic centimeters.

As the condition was inoperable, the patient was discharged. With the amputated specimen, she was presented before the Philadelphia Pathological Society in January 1925.[4] It has not been possible to determine the subsequent course of events except that she moved to a distant state and later died. Necropsy was not performed.

SUMMARY AND COMMENT

In general, the lesion of the arm followed the conventional course of xanthosarcoma; that is, it succeeded trauma, grew slowly and probably began in the tendon sheaths. In all these respects it conformed to fibrosarcoma. It is likely that the lesion was essentially a fibrosarcoma, with a superimposed or concomitant cholesterol infiltration of the tumor cells. Metastasis to such a solitary area as the facial bone must arouse skepticism as to the genuineness of a sarcomatous phase in the facial lesion. With a knowledge of the propensities of the bones to become involved in other expressions of the hypercholesteremic diathesis (Christian's disease), it is reasonable to wonder whether the facial lesions were purely xanthomatous and not necessarily xanthosarcomatous. The apparent absence of visceral metastasis does not help toward a decision, for the relatively benign habits of fibrosarcoma and xanthosarcoma would permit the presence of such small lesions in the lungs and liver that they could not be recognized until necropsy. However, the comparatively rapid progress of the facial swelling and the multiplicity of nodules of the skin of the face and oral mucosa gave stronger evidence for sarcoma in the facial lesions than any other presented.

The manifestations in the cholesterol were not convincing. A value of 177 mg. per hundred cubic centimeters may be regarded within the normal limits, and the second figure obtained, i. e., 132 mg., is even below the lower limit of normal. This would suggest that cholesterol-producing processes were not present when the sample of the patient's blood was taken. (There is evidence that there may be periods during which waves or surges of cholesterol occur in the blood stream, as in untreated diabetes and pregnancy and at the climacteric.) That this

4. Sunderman, F. W.: Xanthosarcoma, Proc. Path. Soc. Philadelphia **27**:88 (Jan.) 1925. Dr. Sunderman followed the clinical course of the patient.

possibly was true is suggested by the patient's testimony that during a pregnancy which developed two years after the beginning of the tumor, multiple yellow tumors appeared over the entire body. She stated that at that time there were masses on the uterus and that a cesarean section was performed.

In any event, it is clear that extensive xanthomatous infiltration can take place in the mucous membrane of the mouth and in the underlying tissues of the face independently of coincident cutaneous manifestations. This case is also an example of the possibility that xanthomatous lesions can exist in the absence of hypercholesteremia.[5] However, this does not exclude the possibility that hypercholesteremia might still occur intermittently, the xanthomatous lesions persisting during the remissions owing to the slow absorption for which cholesterol is noted.

MALIGNANCY IN XANTHOSARCOMA

In a consideration of the malignancy of xanthosarcoma generally there are difficulties if one confines oneself merely to abstracts of the literature on the subject, such as those of Tourneaux [6] and Krogius.[7] Broders' [8] report of seventeen cases, in which he stressed benignancy in "benign xanthic extraperiosteal tumors of the extremities," while suggestive, does not bear strictly on the subject of sarcoma. Each of the seventeen lesions contained lipids and blood pigment; since Broders was not concerned with the general systemic lipoidal phase of the situation he did not state whether the yellow color was referable more to fat or to blood pigment. However, since he emphasized trauma, old hemorrhage and blood pigment in sections, and since foam cells were present in only 64 per cent of the cases, it is clear that he used the term "xanthic" in the objective rather than in the pathologic sense, i. e., not necessarily "xanthomatous." In his opening sentence Broders said, "pertaining to, or tending toward a yellow color."

But even omitting Broders' cases as instances of sarcoma the impression still exists that xanthosarcomas, like all tumors of the tendon sheaths, are relatively benign, to which I agree. However, Krogius challenged this opinion; he believed that, while xanthosarcomas are admittedly at a

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5. Schaaf, F.: Metabolism of Lipids, Zentralbl. f. Haut- u. Geschlechtskr. **35**:193, 1930.

6. Tourneaux, J. P.: Sarcoma of the Tendon Sheaths, Rev. de chir., Paris **47**:817, 1913.

7. Krogius, A.: Xanthosarcomas in Tendon Sheaths, Finska läk.-sällsk. handl. **64**:102, 1922; abstr., J. A. M. A. **79**:173 (July 8) 1922; Acta chir. Scandinav. **55**: 363 (Dec. 22) 1922.

8. Broders, A. C.: Benign Xanthic Extraperiosteal Tumor of the Extremities Containing Foreign-Body Giant Cells, in Collected Papers of the Mayo Clinic, Philadelphia, W. B. Saunders Company, 1919, vol. 11, p. 1032.

low level of malignancy, they are not so strictly limited neoplastically that they do not metastasize. Thereupon I analyzed the original reports of cases in the light of the pathologic, and particularly the histopathologic, examination, the results of which are presented later. Krogius complicated the situation at the outset by including not only fibromas of the extremities but also a myxosarcoma, and as his report has been abstracted in American literature, there is an additional reason why the relations between xanthoma and xanthosarcoma should be reexamined in order to correct any erroneous impression that may have arisen.

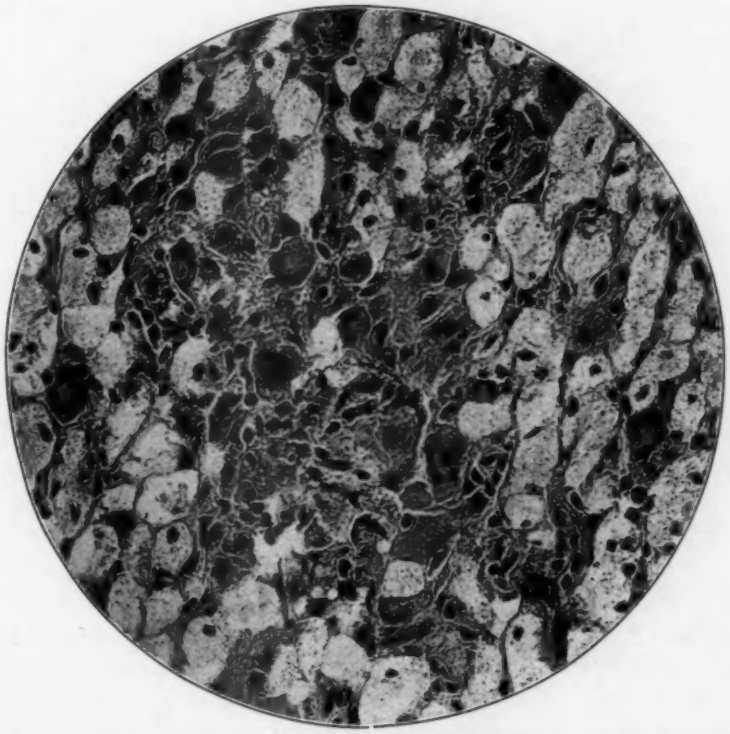

Fig. 8.—Xanthosarcoma: section illustrating nonxanthomatous giant cells and their source in fibrous tissue cells. The formative cell in the circle still shows a cloddy, comparatively nongranular type of cytoplasm which bespeaks its connective tissue composition.

To begin with, Krogius' own series of five cases included but one instance of recurrence; there were no metastases. In his survey of the literature, he cited Tourneaux's compilation of ninety-three cases, leaving the impression that Tourneaux was reporting xanthosarcomas. Reference to the original publication discloses, however, that Tourneaux

did not mention "xantho" in his entire article. Furthermore, in his histologic report he did not describe cytoplasmic degenerations or indicate any in the illustration which would suggest xanthomatous phases.

However, conceding that histologic limitations of Tourneaux' (1913) report did not exclude xanthomatosis, it is most doubtful if any of the growths were xanthosarcomas. Tourneaux collected reports of six instances of metastasis; incidentally, Harbitz [9] also, in turn, cited them. However, on consulting the original communications, of which only three were available (Tourneaux' references are inadequate), it was found that they did not bear out the claim that even nonxanthomatous fibrosarcomas metastasize. Thus, referring to the metastasis in his case, Bolognesi [10] stated no more than that "one year later his brother advised us of his death from a malignant disease with vomiting of blood, extreme weakness, and yellow discoloration of the skin." This is anything but convincing that xanthomatous disease in the lungs was the cause of the vomiting of blood, particularly if jaundice was present. The patient may have had esophageal hemorrhoids.

The report from the Heidelberg Clinic [11] was in telegraphic style; its extent was two lines: "Myxosarcoma of fascia lata. Extirpated. Three months later inoperable recurrence and metastasis to lungs." Myxosarcoma is far removed from xanthosarcoma.

The third citation was an obvious clerical error. All that Degorge [12] stated was that "the patient was seen recently and does not show any recurrences." The tumor was a "fusocellular tumor with giant cells." Tourneaux' ninety-three cases, then, lamentably fail on close analysis to reveal a single example of authentic metastasis of xanthosarcoma. Furthermore, the inadequacy of the evidence is disconcerting, particularly since the erroneous impressions passed through the hands of Tourneaux, Krogius and Harbitz.

Krogius also cited Gaudiani's [13] cases of primary sarcoma of tendon sheaths and its widespread metastases. The statements concerning the latter were valid. Histologically, however, I found that the sarcoma did not qualify as xanthosarcoma; the illustrations depicted alveolar spindle cell sarcoma. The histologic picture was the same in the primary tumor of the groin and in the metastases to the myocardium, the skin and the intestines. There were a gigantic lesion the size of an orange on the dura mater and metastases to the iliac and perirenal regions.

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9. Harbitz, F.: Tumors of Tendon Sheaths, Joint Capsules and Multiple Xanthoma, Arch. Path. **4**:507 (Oct.) 1927.

10. Bolognesi, B.: Globo-Cellular Sarcoma, Thèse de Paris, 1881, p. 29.

11. Report from Heidelberg Clinic, Compt. rend. de Clin. de Heidelberg, 1901, p. 209; 1902, p. 237.

12. Degorge, quoted by Tourneaux.[6]

13. Gaudiani, V.: Primary Sarcoma of Tendon Sheaths: Single Case Report, Policlinico **13**:547, 1906.

Thus, Krogius' rebellion against the relative benignancy of xanthosarcoma subsides when one analyzes the original reports in the light of xanthosarcoma in its strict sense, and Broders' conclusions as to the relative benignancy of periosteal xanthoma must also apply to xanthosarcoma. Even for fibrosarcoma (nonxanthomatous), the instances of widespread generalization narrow down to the solitary case of Gaudiani. That local metastasis of fibrosarcoma occurs, to the

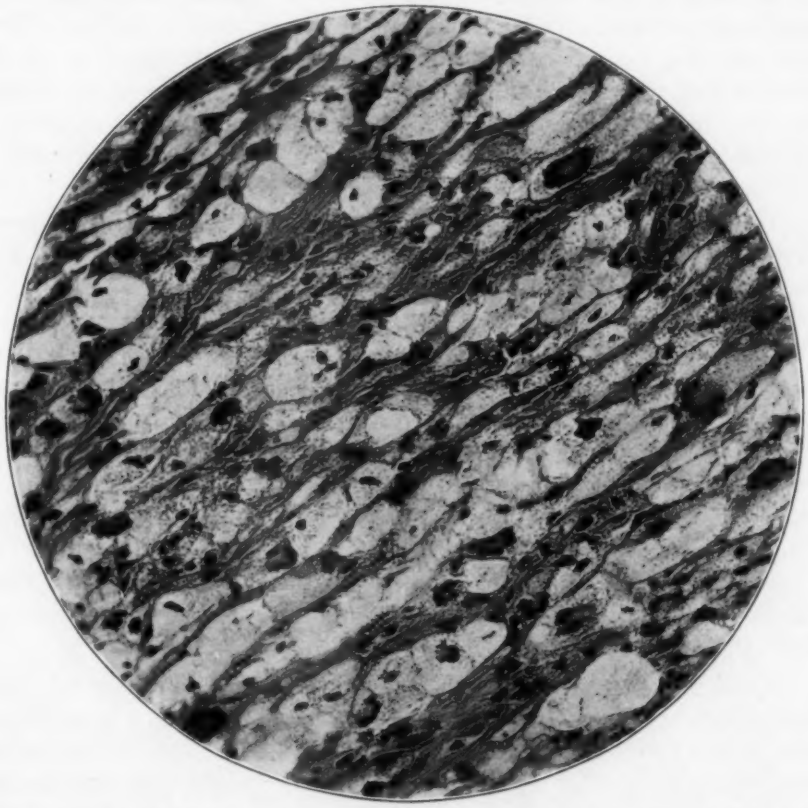

Fig. 9.—Xanthosarcoma: section from deeper parts of the "fungus growth." The genesis of xanthoma cells from fibrous tissue cells is illustrated. Their original arrangement as part of the connective tissue bundles is still maintained.

extent of regional involvement of the lymph nodes and local recurrence, is conceded. In any event, metastases as distant as from the extremity to the face, as in the case reported here, appears to be unknown heretofore for xanthosarcoma, and is seldom seen in fibrosarcoma, as in Gaudiani's case.

The review of the literature disclosed a further misapprehension. Tumors were denominated xanthomatous in the absence of microscopic

examination; the mental reservation should be made in this connection that necrosis, hemorrhage and pigmentation can impart a yellow color to sarcoma. This is important to remember in evaluating the older reports of xanthomatous lesions, and will be elaborated further in respect to modern practice.

Turning from the subject of metastasis to essential malignancy, one may assume tentatively that, contrary to some recent pronouncements, true xanthosarcomas are like fibrosarcomas; locally they are malignant, whether in connection with tendon sheaths or not. They infiltrate and destroy tissue locally and recur on excision, but do not tend to distant metastasis. The lesions in the hard palate of the patient reported here grew so rapidly and were so yellow that they could have been only xanthosarcomas; if this diagnosis is accepted, in the absence of confirmatory histologic examination of the metastatic lesion, I may be recording a case of distant metastasis of xanthomatous sarcoma that is perhaps unique. An alternative (pluricentric) mechanism will be discussed later.

The case of "Xanthofibrosarkom der bursa subachillae anterior" reported by Hünermann[14] was one of the earliest authentic cases; Aschoff saw the sections and confirmed the diagnosis of a giant cell xanthosarcoma. It was "relatively benign, but liable to recurrence." Following local excision it recurred in the scar in four weeks. There was no recurrence after amputation at the middle of the thigh. This may be accepted as the "type diagnosis" of xanthosarcoma. Further clinical details are available in papers by Harbitz,[9] Bloodgood,[15] Broders,[8] Krogius[7] and Kammer.[16] The last mentioned study is probably the classic work of its time, because conducted under the supervision of Aschoff.

Xanthomas of Mucous Membranes.—Tumor-like masses of xanthomatous change analogous to those in the case reported here are very rare in the literature. Only Lebedew[17] described a case which had a resemblance to it. The lesions, which appeared to be granulomas, began in front of the shoulder, extending thence to the face, to the hips, around the waist, on the thighs and around the knees. The largest ones became ulcerated. As to the mucosal involvement, there were yellow nodules in the soft palate sufficiently large to displace the uvula. Lebedew's color plates brought out the reddish yellow qualities of the

14. Hünermann, T.: Ueber einem Fall von Xanthofibrosarkom der Bursa subachillae anterior, Deutsche Ztschr. f. Chir. **182**:410, 1923.

15. Bloodgood, J. C.: Xanthomas, Arch. Surg. **8**:882 (May) 1924.

16. Kammer, E.: Giant Cell Xanthosarcoma, Inaug. Dissert., Freiburg, 1909.

17. Lebedew, A. J.: Xanthoma Multiplex Pseudo-Diabeticorum with Xanthomatous Lymphadenitis, Dermat. Wchnschr. **59**:1343, 1914.

nodules on the forehead, eyebrows and nose and in the mouth. He described the nodules as bluish red at first; later they became yellow in the center. These inflammatory changes were strongly suggestive of the xanthomatous lesions in diabetes mellitus, the dermatologic aspects of which are characteristically different from those of other forms of xanthoma. Lebedew summarized his case as one of a condition simulating xanthoma diabeticorum, but without diabetes. The cholesterol concentration of the blood was not reported.

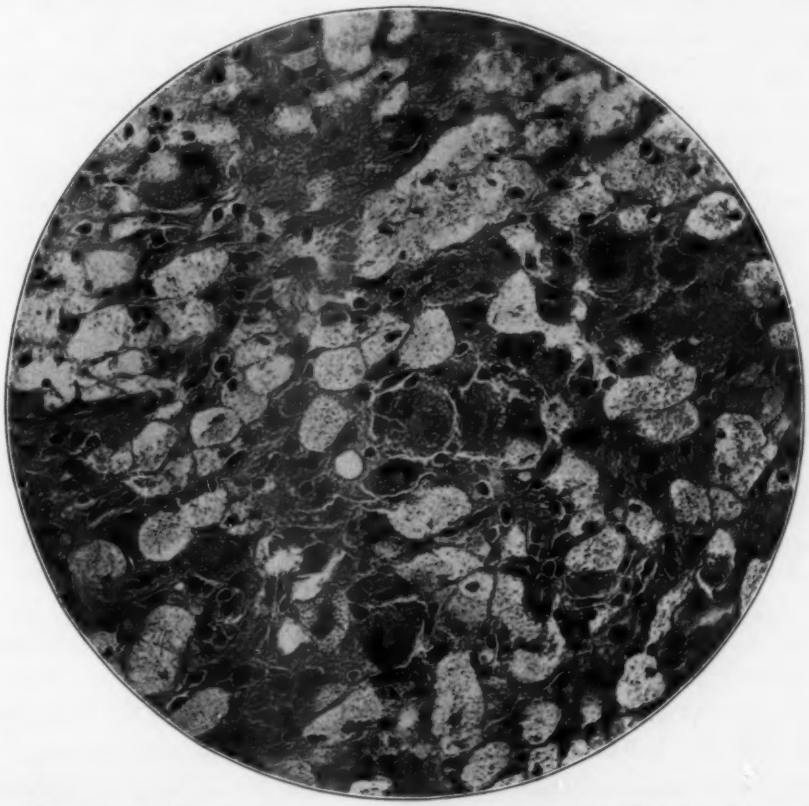

Fig. 10.—Xanthosarcoma: a mixture of mononuclear and multinucleated cells, some in the course of being xanthomatous.

A further instance of xanthoma of the mucous membrane, which came under my observation at necropsy, was a case of involvement of the epiglottis in a man who died of carcinoma of the stomach and a regressive xanthoma in the pons. Previously the lesion had been observed bronchoscopically. This case is reported elsewhere in detail,[2] with a full compilation of reports of cases of xanthoma of the mucous mem-

brane; more or less diffuse plaques on the gums and hard palate have been observed frequently.

Tumor of the Acoustic Nerve.—This lesion, sometimes cholesteatomatous, occupies the cerebellopontile angle. I have introduced this subject on account of the proximity of my patient's facial lesion to the temporal bone, which is intimately associated with tumors of this nerve. Weidman and Schaffer have abstracted elsewhere [2] the point of view of the neurologist, including the connection which tumors of the acoustic nerve have with molluscum fibrosum, xanthoma of the skin and neurofibroma of other parts of the body. Obviously these considerations have a direct bearing on the question of metastasis and pluricentric development of tumors, which will be elaborated later in this paper.

In the case reported here, however, an acoustic phase can be eliminated, because roentgenograms showed that the petrous portion of the temporal bone was perfectly preserved; a tumor of the acoustic nerve sufficiently large to have occupied the antrum would surely have invaded its favorite terrain, the petrosa. The major focus of obstruction of bone appeared to be around the root of the last molar tooth on the right side of the upper jaw.

Some General Systemic Aspects of Xanthomatous Processes.—In 1910, when Chauffard [18] and his co-workers announced a hypercholesteremia in connection with xanthomatous changes, a new trend of thought was developed, and up to the last two or three years cholesterol has dominated the subject of xanthoma etiologically. This is not surprising when the blood cholesterol content may increase almost tenfold (to 1,035 mg. per hundred cubic centimeters and more) in a case of xanthoma tuberosum. In such a case the cholesterol, being thus in excess, should be deposited in the cutaneous lesions. It has always been appreciated, however, that other lipids were associated. Weidman and Freeman [19] stated:

> All of these bodies have not been demonstrated in every case of xanthoma reported—cholesterol has been infrequently reported on the basis of histologic examination, but on chemical analysis of lesions it appears to be constant. (It should be recalled that cholesterol exists amorphously as well as in crystalline form.) Neutral fats appear constantly. They are readily demonstrated by Sudan III and scharlach R, but usually not by osmic acid; that is, they are not the glyceroles of such unsaturated fatty acids as the oleates of normal human fats.

18. Chauffard, A., and Laroche, G.: Pathogénie du xanthelasma, Semaine méd. **30**:241, 1910.

19. Weidman, F. D., and Freeman, W.: Xanthoma Tuberosum, Arch. Dermat. & Syph. **9**:149 (Feb.) 1924.

Recently, however, attention has been called to the blood fats as a group.[20] More and more, it is appreciated that the disturbance is one of the entire group of blood fats, and not of cholesterol in particular. Eckstein's conclusion that "the nature of the lipids in xanthoma is more dependent upon the activities of the tissues than upon the nature of the blood lipids" doubtless applies with special force to this case of xanthosarcoma. His statement is probably not so binding in the non-neoplastic xanthomatous infiltrations such as residual abscesses; when considering neoplasia such radically different circumstances are encountered, particularly involving metabolic conditions, that it becomes a duty to discover whether the processes established for non-neoplastic growth and metabolism are still operative.

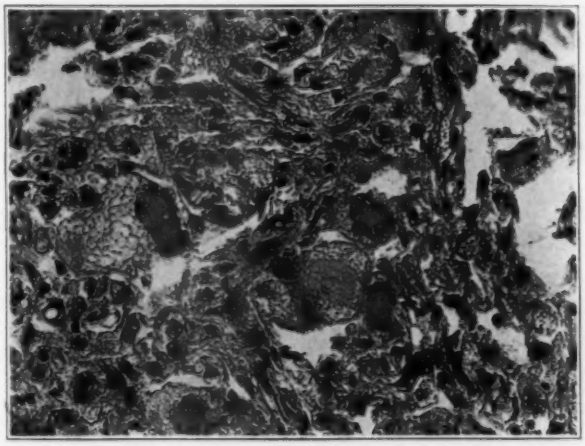

Fig. 11.—Xanthosarcoma: the fibrous portion, demonstrating the fatty granules within the fibrous tissue cells and the foamy cytoplasm of the giant cells.

Lipoidosis in Malignant Processes.—As a disturbance of fundamental metabolism, little is known of the pathologic interrelationships which are peculiar to lipids as they affect malignant cells. But it is known that neoplasia is essentially a matter of growth and that cholesterol is not alone a constant constituent of all cells but one which affects at least the fragility of red blood cells and, linked with vitamin D, is a pronounced factor in growth. Luden [21] probably had such thoughts when

20. Wile, U. J.; Eckstein, H. C., and Curtis, A. C.: Lipid Studies in Xanthoma, Arch. Dermat. & Syph. **19**:35 (Jan.) 1929. Eckstein, H. C., and Wile, U. J.: Lipid Studies in Xanthoma, J. Biol. Chem. **87**:311 (June) 1930. Curtis, A. C.; Wile, U. J., and Eckstein, H. C.: Involution of Cutaneous Xanthomata, J. Clin. Investigation **7**:249, 1929. Schaaf.[5]

21. Luden, G.: Studies on Cholesterol: VI. Value of Blood Cholesterol Determinations and Their Place in Cancer Research, Canad. M. A. J. **12**:147, 1922.

she emphasized the place for cholesterol determinations in research in cancer. White [22] regarded the cholesterol crystals which he found so abundantly in cancer as the product of the cancer per se and not of secondary degenerative processes. The capacity of cholesterol, too, to augment experimental cancer in rats challenges interest; but one cannot speculate further because the very xanthosarcomas which presumably contain so much cholesterol are not notably malignant.

Partition of Lipids in Xanthosarcoma.—"Partition" refers to estimation of the differing proportions of cholesterol, cholesterol esters, neutral fat, phosphatides and so forth, which comprise the entire group of lipids, a procedure similar to the partition of nitrogen in the urine in relation to its ammonia and urea fractions, which has become a method in medicine. In view of the fact that necroses were not noted in the xanthosarcoma which I studied (nuclear degenerations and liquefaction were absent), it was believed that a fairly close estimate of the basic lipoidal metabolic products of the sarcoma cell could be made.

White contributed information concerning the different lipids in malignant tumors. He found that cholesterol and fats occurred regularly in them. Studying the melting points and the behavior toward polarized light in frozen sections on the warm stage of the microscope, he divided the crystals into five groups. Their composition was as follows: (*a*) cholesterol (almost pure); (*b*) a mixture of cholesterol and fatty acids (and alcohol or lecithin); (*c*) neutral fats (often containing fatty acids); (*d*) mixtures of cholesterol with fatty acids (or lecithin and glycerin, etc.), and (*e*) the same composition as *a*, *b* and *d*, but different in certain details of morphology.

Almost every carcinoma that White examined contained crystals *d* or *e*, sometimes associated with *a*, *b* and *c*. Since they did not occur as a rule in necrotic areas, he concluded that they were associated with the proliferation of cells rather than with their degeneration; therefore "it is suggested that cholesterin may be associated in some way or other with the regulation of cell proliferation." (Incidentally, Roffo [23] found as much as three times more cholesterol in cancerous tissue than in the rest of the animal. He reemphasized the ability of cholesterol to take up water—something which may mean much in the water and other metabolism of cells.) Crystals *d* and *e* also occurred in sarcomas (sarcoma of the femur, melanotic form).

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22. White, C. P.: On the Occurrence of Crystals in Tumours, J. Path. & Bact. **13**:3, 1909.

23. Roffo, A. H.: The Cholesterol Ratio in Tumors, Prensa méd. argent. **11**: 1060 (April) 1925; **11**:28, 1924.

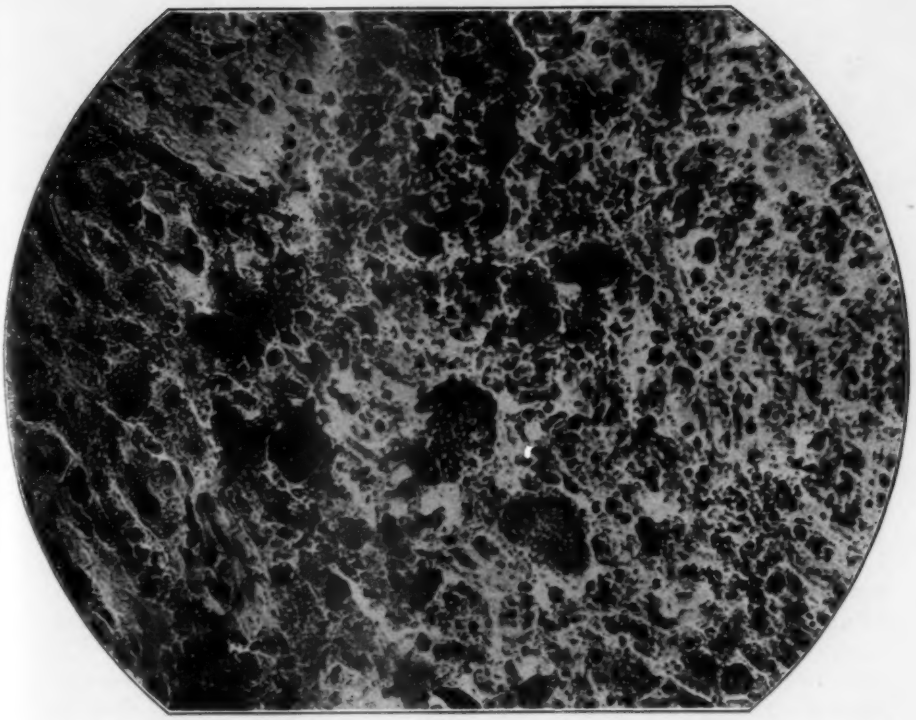

Fig. 12.—Field 2: mixed (arc) light; green and yellow filter. This gives a good general perspective of the entire composition of the section.

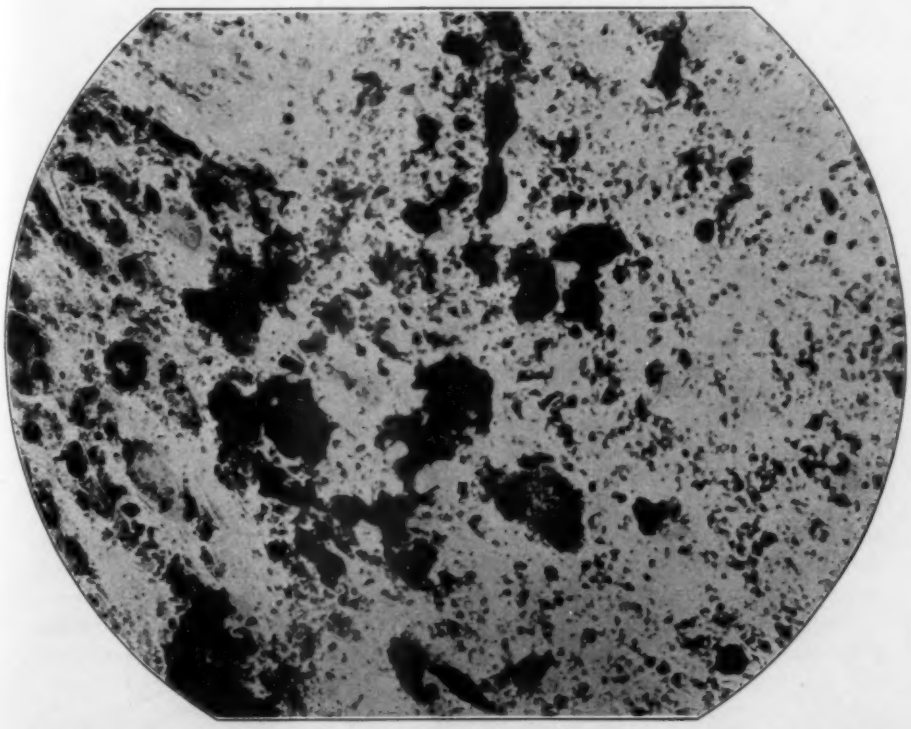

Fig. 13.—Field 2: mixed (arc) light; blue filter. Only the neutral fats stained with sudan III are registered.

White's studies thus indicated that polarized light was not available for quantitative chemical analysis of the different fatty substances; only one of the five crystals that he classified was pure, and probably the amorphous masses were likewise mixtures. Thus only the isotropic substances could be identified with certainty as a group of lipids totally apart in any one respect from another group. Unfortunately the contrasting group of anisotropic particles (containing isotropic substances also) do not justify comparison because they are so indefinitely composed, quantitatively; their indefiniteness disturbs any attempt at mathematical comparison.

Even in 1909 White realized the rôle which the factor of "mixture" played in maintaining lipids in solution:

> Apparently these substances help to keep one another mutually in solution in the body fluids, from which they may, under certain conditions, separate in the crystalline form. It has long been known that lecithin forms a fine emulsion or a colloidal solution in water, and it does this because of the cholesterin which it contains. When freed from cholesterin it no longer becomes emulsified with water. Similarly, cholesterin mixed with fatty acids forms a fine emulsion with water, especially if a trace of alkali be present. These emulsions or colloidal solutions are unstable, being easily precipitated by the addition of acids or salts.

This statement antedates some of the pronouncements of Schaaf [5] by twenty years.

As to the xanthosarcoma reported here, information was especially desired concerning the lipid partition of cells in the more central parts of the tumor as compared with the partition of those at the periphery. It was conceivable, assuming that the peripheral parts were growing more actively than the central ones, that there would be an absorption of neutral fats from the central parts of the tumor (neutral fats and soaps being more readily absorbed and removed) and that the residue of cholesterol would be greater in the center than at the periphery. It was thought that an approximation could be obtained on the basis of singly refractive and doubly refractive substances, together with the behavior of the substances toward staining with sudan III. Accordingly, emulsions were tested by these methods, as follows:

> Samples of tissue were taken from ten portions of the tumor: (1) interosseous fibrous tissue, (2) the most central parts of the tumor, (3) the summit of the fungus growth (superficially ulcerated), (4) the fibrous capsule, (5) the central part of the tumor, (6) aerolar fat, (7) muscle, (8 and 9) the peripheral advancing part of the tumor (two portions) and (10) a portion at the junction of the fibrous center and the definitely xanthomatous part. The latter block of tissue was selected to represent as closely as possible the zone of transition between the more fibrous portions in the interosseous membrane and the more definitely xanthomatous parts peripherally. The positions of the various portions are indicated in figure 2.

The samples of tissue from the different parts were ground up, emulsified in water and examined after being stained with sudan III and by polarized light. Other portions of the emulsion were extracted in hot alcohol, filtered, evaporated to small volume and similarly examined. The latter procedure was necessary to avoid the intermixture of collagenous and other fragments which were also doubly refractive and which in their finely subdivided state could be distinguished from fatty substances with difficulty.

Anisotropic substances in significant quantities occurred only at one position, i. e., at the summit of the fungus-like growth, where superficial ulceration had taken place. Elsewhere the quantities of anisotropic substances were negligible. In short, almost all of the fatty substances were neutral fats. It was surprising that the normal areolar fat contained as much anisotropic material as the tumor, even in the ulcerated, superficial part just mentioned. Thus the composition of the tumor was found to be comparatively uniform as between isotropic and anisotropic substances; it was estimated that less than 1 per cent of the lipids were doubly refractive.

Cholesterosis of the General Body Fat.—That hypercholesterosis, as seen in endothelium and in white fibrous tissue cells of xanthoma, could also occur in other, normal tissues which contain fat (fatty areolar tissue) was suggested by White's work in which he showed that the fatty globules and crystals were seldom chemically pure neutral fat or chemically pure cholesterol, but mixtures. This held good even for fat in crystalline form. While repeated crystallization makes for purity of a chemical substance, the converse is not true. A crystalline form does not guarantee chemical purity.

After White's conclusions it was only a short step to the question whether, under certain conditions of hypercholesteremia, the cholesterol and other lipids could pass into solution in normal fatty areolar tissue. For example, certain authors have reported that fatty crystals occur in otherwise normal areolar tissue, as Gray [24] found in his work on sclerema neonatorum and Proescher and Meredith [25] in their study of myxolipoma.

As to the case reported here, normal areolar fat at a distance of 2 or 3 mm. from the xanthosarcoma contained numerous anisotropic crystals. However, this fact could not be invoked as evidence of widespread systemic cholesterosis of fat, because diffusion could account for it, i. e., local absorption from a nearby focus of such extreme

24. Gray, A. M. H.: Sclerema Neonatorum, Arch. Dermat. & Syph. **14**:635 (Dec.) 1926.

25. Proescher, F., and Meredith, E. W.: Multiple Myxo-Cholestro-Lipomata, Surg., Gynec. & Obst. **9**:578, 1909.

Fig. 14.—Field 1: polarized light; green and yellow filter.

Fig. 15.—Field 1: polarized light; blue filter.

fatty change. Fat 2 or 3 cm. away contained even fewer anisotropic crystals. Fat from the palm showed negligible quantities of this substance.

Thus it appears that even in tissue preserved for several years in formaldehyde, anisotropic fat did not occur in the general areolar fatty tissue. Small quantities diffused outward for short distances from the xanthosarcoma.

XANTHOMATOSIS IN TUMORS OF THE CONNECTIVE TISSUES

Sufficient has been said already about xanthomatous examples of the commonplace fibromas—fibrosarcomas of tendon sheaths—based on the compilations of Tourneaux, Krogius, Harbitz and Bloodgood. The accompanying table is designed mainly to indicate the range of other tumors which may be affected by xanthomatous changes.

I wish to call attention to what has been stated already about the basic pathologic process of foam cell tumors, i. e., that there are probably good reasons for regarding some of the tumors in the succeeding table as composed of cells which are "fundamentally, metabolically" lipoidal in nature, such as the xanthomas of tendon sheaths. In the case of tumors having an endothelial basis, such as hemangiomas and lymphangiomas, the presence of cholesterol may well be a secondary, more or less accidental addition. Lubarsch [26] advocated a special nomenclature to apply to these, recommending that they be called "fibroma xanthomatosum," "lymphangio-xanthomatosum," etc. That is, the designation "xantho-" would be used to indicate that the intrinsic cells of such tumors were not fundamentally lipoidal any more than *Herzfehlerzellen* are fundamentally pigmentary.

It is appreciated that some of the tumors listed may overlap biologically, as the nomenclature of one author may not coincide with that of another. The "granulation tissue" tumor of Garrett, for example, may well be chronically inflammatory and not at all neoplastic. I think that this is true in the case reported by Lebedew. However, the diagnoses of the different authors have been taken at face value, and it has been left to the reader to appraise the interrelationship of the different lesions listed.

The table gives a general perspective of the range of tumors or quasitumors which may be affected by xanthomatous change. Further insight may be gained by the few comments which follow.

Granulation Tissue Tumors (Garrett [1]).—It must be conceded at the outset that these were not neoplasms. In a symposium on xanthomas, opened by Bloodgood,[15] two of his pupils (Garrett [1] and David T.

26. Lubarsch, O.: Generalisierte Xanthomatose bei Diabetes, Deutsche med. Wchnschr. **44**:484, 1918.

Smith [27]) read papers. In their nomenclature these workers did not adhere to "xanthoma" in its pathologic sense; they even included some tumors which were apparently not even pigmented. Thus, of twenty-six "granulation tissue tumors" studied, only one was xanthomatous. Garrett admitted that they were a "heterogeneous group." Microscopically, they exhibited "hemorrhagic areas and lymph cells and leukocytes which suggested infection." In my opinion it was a mistake to include them among the xanthomas; however, the meaning of xanthoma for the surgeon may be founded on something additional clinically of which I am unaware; hence the data are included here for what they may be worth.

Xanthomatous Tumors of the Connective Tissues Reported in the Literature

Authors	Type of Tumor	Miscellaneous Data
Garrett [1]	Granulation tissue tumor	One xanthic tumor of twenty-six studied
Broders [6]	.....	Seventeen extraperiosteal tumors
Lebedew [17]	.....	Multiple tumors (diabetic ?)
Henschen [26]	Neurofibroma (some cholesteatomas)	Cerebellopontile angle (tumors of the acoustic nerve)
Proescher and Meredith [25]	Myxolipoma	Widespread; subcutaneous and internally
Garrett [1]	Capillary angioma	Knee
Petri [30]	Hemangioma cavernosum	Muscularis of the intestine
Kirch [21]	Lymphangioma	Knee (two cases)
Garrett [1]	Fibrohemangioma	Xanthomatous (nineteen of seventy-six cases studied)
Wessen [33]	Fibroleiomyoma	Intrathoracic (retropleural)
Kirch [21]	Endothelioma	Dura
Smith [35]	.....	Parotid
	.....	Dura
	Lymphangio-endothelioma	Tongue; vulva
Harbitz [9]	Sarcoma* (giant cell) (polymorphous cell)	Tendon sheaths and capsules of the joints
Tourneaux [6]	Fibroma and fibrosarcoma	Most common xanthomatous tumor
Krogius [7]	.....	Tendon sheaths
Harbitz [9]	.....	
Kirch [21]	.....	
Gast and Zurhelle [36]	.....	Thigh

* Dietrich's case of fibroxanthosarcoma of peculiar distribution is not valid.[2]

Broders' seventeen benign xanthic swellings of the extremities have already been mentioned. It need only be added that the extent of xanthomatous change varied widely in the different lesions (present in only 64.7 per cent), yet fat was demonstrated in all of them by means of special fat dyes. There is a possibility that the remaining 35.3 per cent exhibited xanthoma cells at an earlier period, but became regressive, in keeping with the propensities of xanthoma, leaving behind, however, a certain residue of unabsorbed fat. It remains uncertain, however, whether some of the fat could have depended in any way on an associated hypercholesteremia or was entirely referable to disintegrated

27. Smith, D. T.: Method for Making a Differential Diagnosis Between Xanthomatous and Melanin Tumors from Frozen Sections, Arch. Surg. **8**:908 (May) 1924.

Fig. 16.—Field 2: polarized light, no light filter. The crystals registered partly red, owing to intermixed neutral fats which overlaid the anisotropic crystals and tinted the light rays after they had been refracted by the crystals.

Fig. 17.—Field 2: polarized light; red filter. The red rays (fig. 16) have been blocked out, Hence, a true registration of anisotropic substances is seen, which was not the case in figure 16.

erythrocytes; no data were submitted bearing on this point. Therefore, these seventeen "tumors" resolve themselves in principle into peculiar pigmented scars which may or may not have exhibited foam cells of the order of those seen in arterial atheroma.

The report of Lebedew's case in which numerous tumor-like masses of granulation tissue occurred in the mouth and on the skin has been abstracted in full in a previous section of this paper.

Neurofibroma.—I refer here to a particular example, i. e., tumor of the cerebellopontile angle (tumor of the acoustic nerve), described in full by Henschen.[28] Details may be found elsewhere.[2] Some of these tumors contain so much cholesterol that they have received the name cholesteatoma. In one case they were found associated with xanthomas of the skin (Delore[29]).

Myxolipoma.—This was an extraordinary neoplasm occupying almost the entire abdominal cavity, associated with similar tumors in the calf, groin, breast, pleura and lung and on the surface of the liver. Microscopically it consisted of stellate cells together with round cells which contained fat. Doubly refractive crystals were found in the fatty materials. It was probably a pluricentric myxolipoma originating in subserous and subcutaneous fat. The intermixture of doubly refractive substance was small; a determination of the blood cholesterol was not made, nor was "normal" fat from remote parts of the body tested. It would be interesting to know whether the anisotropic fat observed in this tumor was present simply as a part of the general lipoidal storage processes in the normal and otherwise fatty parts of the body.

Capillary Angioma.—One such tumor, in a joint, was encountered by Garrett in the studies already mentioned. Pigment was associated with the foam cells.

Hemangioma Cavernosum.—This was a tumor the size of a nut in the muscular tunic of the ileum, exhibiting yellowish white points which were xanthomatous histologically. The fat occurred in the hyperplastic endothelium of the blood spaces. Incidentally, the patient had cancer of the gallbladder, suggesting strongly that hypercholesteremia was present. Petri[30] concluded that almost all kinds of cells, in addition to fixed connective tissue cells, can probably become xanthic.

Lymphangioma.—Kirch[31] saw two polycystic lymphangiomas of the knee, each about the size of an egg. The endothelial linings of the

28. Henschen, F.: Histology and Pathogenesis of Tumors of the Cerebellopontine Angle, Arch. f. Psychiat. **56**:20, 1915.

29. Delore, cited by Henschen.[28]

30. Petri, E.: Zur Kenntnis der xanthomatösen Gewebsumwandlung: Haemangioma xanthomatosum, Centralbl. f. allg. Path. u. path. Anat. **34**:1, 1923.

31. Kirch, E.: Xanthomatous Tumors, Klin. Wchnschr. **3**:1425, 1924.

spaces contained the fat, which was responsible for the yellow color; hence fibrosis is not a sine qua non for xanthoma. Kirch's communication may be regarded as a model in the investigation of xanthomatous tumors; he examined the blood cholesterol values in eight cases, with the following results:

	Cholesterol, Mg. per 100 Cc.
Polycystic lymphangioma	302 to 313
Polycystic lymphangioma	256.7
Endothelioma of the dura	481
Fibrosarcoma of the thigh	190 to 173
Fibrosarcoma of the leg	255
Sarcoma of the arm	450
Fibrosarcoma of the ankle	179 to 284
Giant cell granuloma of the finger	187

Furthermore, he found that even after the surgical excision of a tumor the blood cholesterol remained high; i. e., the tumor was not acting as a depot for the fabrication of the cholesterol. Kirch's description of the pathologic process of xanthomatosis is a masterpiece; among other things he stated that "neoplasms of most diversified localization and kind can become xanthomatous, even epithelial ones."

Fibrohemangioma.—Garrett studied the impressive number of seventy-six fibrohemangiomas, of which nineteen were xanthomatous. I think that hemangiomas, of all tumors, need least association with general hypercholesteremia to explain their xanthomatosis. With red blood cells so rich in cholesterol and with such opportunities for stasis and disintegration as occur in hemangiomas, I believe that there is a likelihood of local absorption of cholesterol, just as cholesterol crystals frequently appear around areas of hemorrhage in tumors. That is, xanthohemangiomas are readily explained on the basis of local xanthomas (Stewart [32]); general hypercholesteremia need not be invoked.

Fibroleiomyoma (Wessen [33]).—This was a tumor the size of a grapefruit, occurring intrathoracically, or to be exact, retropleurally. Smooth muscle fibers occurred throughout the tumor and under the capsule. Wessen believed that the tumor had its origin in embryonal derivations, possibly of the esophagus.

Endothelioma.—This lesion, occurring in the dura, was one of the eight xanthomatous tumors described by Kirch. The dura is a rather common seat of xanthomatous change. It is involved in diabetic

32. Stewart, M. J.: On the Cellular Reactions Induced by Local Deposits of Cholesterol in the Tissues, J. Path. & Bact. **19**:305, 1915.

33. Wessen, N.: Xanthomatous Intrathoracic Tumor, Acta chir. Scandinav. **53**:621 (June) 1921.

xanthoma; it was noted by Pinkus and Pick [34] in a case of generalized xanthomatosis; it is commonly involved in Christian's disease (one of the juvenile forms of generalized xanthomatosis) and has been studied by neurologists in connection with tumors of the acoustic nerve. Under these circumstances it is doubtful that a xanthomatous "tumor" of the dura should be regarded as truly neoplastic, for by the time fibrous tissue cells become swollen and otherwise distorted by xanthomatous infiltration it is difficult in most cases to identify the mother cell of the tumor as endothelial or even neoplastic. Many or most dural "xantho-endotheliomas" are doubtless simply xanthomatous masses of hyperplastic endothelium or fibrous tissue.

Lymphangio-Endothelioma.—Carol Smith [35] worked in the laboratory of Pick in Berlin, the center of studies of xanthoma in Europe. He analyzed four cases which had accumulated in Pick's laboratory; of the two lymphangio-endotheliomas included, one involved the tongue and the other the vulva.

Sarcoma.—The various kinds of sarcomas noted in the table, i. e., giant cell and polymorphous cell sarcoma and fibrosarcoma, as well as the fibromas which may be regarded as having undergone xanthomatous change, have been discussed sufficiently in the early portion of this paper. It will be recalled that under critical analysis few were found to exhibit true metastases, whereas regional metastasis to the lymph nodes and local recurrence were noted frequently.

Gast and Zurhelle [36] deserve special mention, however, because in the study of their case of xanthosarcoma of the thigh they analyzed the composition of the fat, finding equal parts of neutral fat and cholesterol. Most cells contained only one kind of fat, while a few contained both kinds. They mentioned hypercholesteremia, although they did not inquire about its presence in their patient. They stated, however, that in the future an antecedent hypercholesteremia must be considered in xanthoma.

PATHOLOGY

Two phases are concerned, the sarcomatous and the xanthomatous. Obviously the general pathologic process of sarcoma will not be considered here. It is sufficient to say that whether the tumor in the case reported here was fibrosarcoma at the beginning or not, at operation it was a mixed spindle cell and round cell tumor.

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34. Pinkus, F., and Pick, L.: Xanthoma and Foam Cell Tumors, with Report of a Case of Generalized Xanthoma Tuberosum, Dermat. Ztschr. **15**:706, 1908.

35. Smith, C.: Histology and Nature of the So-Called Foam Cell Tumors, Surg., Gynec. & Obst. **14**:551, 1912.

36. Gast, E., and Zurhelle, E.: Xanthosarcoma of Thigh, Berl. klin. Wchnschr. **55**:930, 1918.

Metastasis.—A further word must be said on the subject of metastasis in the case reported. The reports in the literature of metastasis of xanthosarcomas have already been reviewed, and only one authentic instance was found. Furthermore, the congener fibrosarcoma metastasizes only exceptionally. In this light judgment must be carefully balanced concerning the facial lesion in my patient. Thus, according to the rule for metastasis of sarcoma, the organs involved should be the lungs, liver and other viscera liable to a rich hematogenous distribution. The deep tissues of the face certainly do not fall in this category.

Fortunately, there is an alternative solution. At this point the reflections of Proescher and Meredith[25] apply because they also reported tumors (multiple myxocholestolipomas) the anatomic location of which was so inconsistent with a hematogenous distribution that they decided in favor of multiple primary tumors. This can apply also to fibrosarcoma and the xanthosarcoma in my case, if the hypothesis already proposed can be permitted, that the xanthosarcoma was basically a fibrosarcoma, with a superadded xanthosis. For example, there are several analogous reports in the literature of so-called metastasis of the fibrosarcoma of the extremities to the dura, which are singularly analogous in principle to the condition in my case; thus my case does not stand alone in respect to this apparent inconsistency in metastasis. Rather, it is in order to think as Proescher and Meredith did, namely, that a pluricentric formation of tumors is concerned in fibrosarcoma and in xanthosarcoma also; as in multiple myeloma, there may be something consistent (in the direction of development of tumors) in the kind of tissue in which the tumor originates, even though it is located in diverse parts of the body.

There was a further consideration in my case that bore on the situation, namely, the history of a possible origin of the facial lesion around or in the socket of a tooth. In dense fibrous tissue like that of the periosteum or the gingivae sequestrums may have maintained a continuous focus of irritation, provoking at least the formation of granulation tissue. Whether this mounted to the proportions of fibrosarcoma or not, the known xanthomatous propensities of the patient assured an opportunity for the development of at least a xanthoma at this site. A full description of scar xanthoma, including locations at the roots of the teeth in Christian's disease, has been given elsewhere.[37]

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37. Weidman, F. D., and Boston, L. N.: Generalized Xanthoma Tuberosum with Xanthomatous Changes in Fresh Scars of an Intercurrent Zoster: Adenocarcinoma of The Ampulla of Vater at Necropsy, Arch. Int. Med. **59**:793 (May) 1937. Weidman, F. D., and Stokes, J.: Extensive Xanthoma Tuberosum in Childhood Due to Infectious Cirrhosis of the Liver, Am. J. Dis. Child. **53**:1230 (May) 1937.

There is thus an accumulation of disconnected angles of the xanthoma-fibroma-sarcoma situation that admit the facial lesion on other than a metastatic basis; there is no heresy in regarding it as a focus metastatically independent of the lesions on the arm and skin.

Xanthogenesis.—Tumors may exhibit the xanthomatous phase in at least two and possibly three forms: First, the phase may be exhibited as an essentially local phenomenon, i. e., as an end-result of simple degenerative and necrotic changes such as can occur in large morbid masses in general. Second, the rôle of an abnormal general fat metabolism, whether hypercholesteremia accompanies it or not, must be taken into account as a force operating on (neoplastic) cells which are admittedly unbalanced metabolically and yet have a threshold high enough to endure ordinary normal fat conditions in the environment. Here the tumor, in becoming xanthomatous, would simply be sharing in and succumbing to the general lipoidosis. Finally, a third form of xanthomatous change can be assumed as the expression of an inherent property of the particular neoplastic cell concerned—a matter of fundamental cellular metabolism peculiar to it, which would endow it with the same properties as those peculiar to a lipoma, except in the differing composition of its fats.

Twenty years ago Carol Smith [35] outlined the pathologic process of xanthoma. He noted that cholesterol appears in tumor cells (and only in those of the connective tissue series) under the following circumstances: (1) when the tumor cells originate in an organ which normally contains cholesterol, i. e., the Grawitz tumor; (2) when the cholesterol is set free in the tumor as a product of degeneration; (3) when the cells assume special metabolic rôles (in the direction of cholesterol). This new property persists in the neoplastic cells. These subdivisions will be considered further. Some of the mechanisms by which xanthomatous changes are produced in tumors are as follows:

Local Xanthomatous Changes.—Among these Stewart [32] included dermoid cyst, cholesteatoma, testicular teratoma and epithelioma. As to the presence of cholesterol, he cited White: "In tumors generally, and especially in carcinomas . . . apart from any necrotic changes." In all of the lesions lipids are liberated locally, independent of the neoplastic cell itself; thereafter, in the presence of fluids surcharged with lipids the neoplastic cells assume xanthomatous features (absorption of cholesterol?).

Globus [38] reported a "teratoid cyst of the hypophysis;" his excellent illustrations leave no doubt of at least some xanthomatous intermixture, although he referred the fatty cells to incomplete development of cells of the sebaceous glands. This was the interpretation that Kaposi, many

38. Globus, J. H.: Teratoid Cyst of the Hypophysis, Arch. Neurol. & Psychiat. 9:417 (April) 1923.

years ago, placed on xanthomas. Pituitary xanthomas have been reported a number of times (as in Christian's disease) and may not be "local." However, in such a richly lipid environment they may properly suggest this origin. Incidentally, Oudendal [39] observed doubly refractive crystals in a sarcoma of the thyroid; he ascribed them to repeated hemorrhages, from which cholesterol crystals developed. He also called attention to the protein Charcot-Leyden crystals, which might constitute sources of error in studies of local xanthomatous residua.

Local degenerative and necrotic changes in a large morbid mass such as a neoplasm can account for some xanthomatous changes which have been reported in tumors. In such a case there is a focus of fatty materials, including such various substances as neutral fats, soap, cholesterol and phosphatides. The imbibition or phagocytosis of these substances by connective tissue and other cells gives rise to the well known foam or xanthoma cells, but, in addition, the fatty substances appear intercellularly. The proportion of the different fats varies in different lesions. In my opinion neutral fats and soaps should be absorbed more readily than cholesterol when free in tissue spaces, and it is to be expected that the proportion of these substances varies largely in a given lesion from time to time, depending on the rate of absorption and particularly on the age of the lesion.

There is no reason why secondary changes of the same order should not occur in lesions which, like xanthoma tuberosum and xanthosarcoma, are conceivably xanthomatous from the beginning, i. e., lesions in which the question of the proportion of the lipids is fundamental and important for a knowledge of their pathologic processes, especially in attempting to reconcile the cellular fatty conditions with those of the blood. In such cases the valid chemical data on the fats, i. e., those representative of the basic process, would be obtained only from the *early* lesions. Therefore, care should be exercised in selecting the materials designed for chemical analysis when it is proposed that the figures obtained for lesions are to be compared or reconciled with those for circulating blood fat or for similar factors in the disordered fatty state.[19]

Essential or Intrinsic Xanthomatosis.—The cell comprising a tumor of a tendon sheath probably should be regarded as a special kind of xanthoma cell, although morphologically it cannot be distinguished from other foam cells (diabetic xanthoma). What special place these cells merit in the classification of xanthomas depends on their fundamentally different genesis. Thus, the cells from which such tumors spring have the inherent, specific property of elaborating cholesterol just as the cells of the adrenal glands have, whereas the other members of the xanthoma

39. Oudendal, A. J. F.: Crystals and Pigments in Living Tissues, Mededeel. v d. burgerl. geneesk. dienst in Nederl.-Indie, 1925, p. 1.

group are supposed to take cholesterol more or less passively into their cell substance; that is, these cells of the tendon sheaths are blastomatously lipoidal. This concept, original with Sick,[40] was disputed by Pick, who preferred to look on all xanthomas as comprised of nonspecific cells (hemangiomas, fibromas, granulation tissue); these cells differed from ordinary tumor cells only in that, more or less secondarily, the lipid substances had become infiltrated. It is assumed that Pick has now departed from his original position and recognizes the concept of the "foam cell" tumor as his pupil, Petri,[41] subsequently described a xanthocarcinoma of the stomach. The tumor cell in Petri's case was (in both the primary and secondary lesions) that of a gastric adenocarcinoma; there were no degenerative changes to permit the interpretation that it was a secondary change in connection with local hypercholesterosis.

Incidentally, in Pick's laboratory careful study was made of the nature of the fat concerned, with the result that doubly refracting substances were not found in this xanthocarcinoma cell; neutral fats were exclusively concerned. I feel, however, that a further statement of Petri —which doubtless is supported by Pick—namely, that the foam cell tumor can contain only neutral fat, is going too far. That it was true in Petri's case of xanthocarcinoma is conceded, but from the observation of a solitary case this property should not be postulated as a constant one for all foam cell tumors. Thus, before reading Sick's paper, I had come independently to the opinion that the tumor in my case belonged in the foam cell group, i. e., that it was not a "symptomatic" or a "local" xanthoma. Contrary to Petri's contention, in this tumor there were demonstrable, although scanty, quantities of doubly refractive substances.

In my opinion the concept of the foam cell tumor is mostly academic from the standpoint of the genesis or basal metabolism of the cell concerned. "Foam cells" in the sense of Sick cannot be differentiated morphologically from xanthoma cells. It is only by estimating the derivation of the cell concerned—whether from the adrenal, prostate, or some other gland—and perhaps by the exclusion of certain forms, such as local and symptomatic xanthomas, that the diagnosis of foam cell tumor can be made. Only when it is finally known just how the fat has developed in a given case of xanthoma will it be possible to make rational subdivisions and arrange a logical classification.

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40. Sick: Ueber Xanthoma und Schaumzellentumoren, mit Bericht eines Falles von generalisierten Xanthoma tuberosum (Discussion), Dermat. Ztschr. **15**:710, 1908. "Foam cell tumor" was Sick's designation; this is obviously inappropriate, because "foam cell" also fits xanthomas other than fundamentally, metabolically lipid ones.

41. Petri, E.: Ein Beitrag zur Kenntnis der sogenannten Schaumzelltumoren, Frankfurt. Ztschr. f. Path. **27**:507, 1922.

Furthermore, it is only with a knowledge of all the involved considerations concerning fatty infiltration and fatty degeneration (applying to neutral fats only, presumably), as outlined by Adami,[42] that the full and proper perspective of the situation can be arrived at. The involved considerations in connection with these subjects also apply to cholesterol and other lipids; the cellular biology of xanthomatous change can never be approached and definitely recorded until it is examined in the same light as "fatty infiltration" and "fatty degeneration."

Summary.—A comparison of the data on benign xanthoma tuberosum, taken as a standard, with those on the xanthosarcoma reported here revealed nothing (particularly morphologically) which indicated any differences in the essentially xanthomatous processes, barring the embryonal cytology to be expected in any sarcoma. The xanthoma cells in my case resembled equally those of xanthoma tuberosum and of Christian's disease. The normal or nearly normal blood cholesterol value for my patient is not significant in any particular direction; it has been noted in numerous cases of non-neoplastic xanthoma.[5]

For this particular case of xanthosarcoma the way is theoretically open to explain the xanthomatous phases in two of the three ways just mentioned. First, this lesion may have been fundamentally a fibrosarcoma; in the presence of a high fat value for the blood the tumor cells absorbed abnormal quantities and became infiltrated by fat. This presupposes a period of hypercholesteremia, which this patient did not have when tested, but probably experienced at other times (there was a clinical history of pregnancy). Or second, the tumor cell may have been faulty in respect to its handling of fats from the beginning and may have been xanthosarcomatous independently of fatty conditions (foam cell tumor of Sick).

Unfortunately, the blood cholesterol values are not definite enough to assist in deciding between the two possibilities. Certainly the factor of degeneration and necrosis, with the production of local xanthomatous depots (as illustrated in old residual abscesses), was not operative in this xanthosarcoma; numerous blocks of tissue were searched microscopically, and there was nowhere a frank degeneration, much less necrosis.

There are no proponents of a theory that the tumors are the source of hypercholesteremia, if this is present. It is doubtful that even such a large depot of cholesterol as this sarcoma could account for the scant increase in the blood cholesterol value by a discharge into the circulating blood. Kirch found that the operative removal of xanthic tumors was not followed by the disappearance of hypercholesteremia.

42. Adami, J. G.: Principles of Pathology, ed. 2, Philadelphia, Lea & Febiger, 1910, vol. 1, p. 20.

For fibromas and fibrosarcomas of tendon sheaths in particular it is natural to wonder what connection their specialized lining endothelial cells, involving as they do a quasisecretion, can have with a cell like that of xanthoma and xanthosarcoma which accumulates cholesterol. Normal synovial fluid contains from 0.06 to 0.07 parts per thousand of fat (Hammarsten [43]). It is sometimes milky and contains degenerating cells, i. e., there are possibilities of the source of cholesterol being immediately at hand. Lubarsch [26] and others independently saw lymphatic stasis as a predisposing factor in xanthomatous deposits; the tendon sheaths, being so highly developed, involve extensively the circulation of the lymph. In the presence of a neoplastic swelling of tendon sheath cells, stasis of the fluid of the tendon sheath is likely to follow and to accentuate whatever xanthomatous tendencies are already established. It is agreed that stasis alone cannot induce xanthomatosis.

While the pathologic process of xanthosarcoma is, thus, definite in many respects, particularly as to the morbid anatomy, it becomes most unsatisfactory when the precise etiology is approached. Furthermore, the prospect of enlightenment is remote in view of the infrequence of cases with which to work.

SUMMARY AND CONCLUSIONS

A fatal case of xanthosarcoma is reported which is almost unique on account of nodules in the oral mucosa and deep tissues of the cheek; while there are some observations which point to metastasis from the lesion on the forearm, it is more likely that the two foci developed independently as the result of separate trauma or as "tumors of multiple origin." Whether metastatic or pluricentric, multiple xanthosarcomas must be given a guarded prognosis; multiple tumors, as in my patient, can acquire a practical prognostic significance comparable to that of metastatic tumors.

Reports of cases of xanthomatous tumors collected from the literature are listed; the growths in these cases include fibroma, neurofibroma, myxolipoma, angioma, endothelioma and sarcoma. Even carcinomas may be xanthomatous.[2]

A photographic method, employing polarized light and different filters, is described for more accurately distinguishing quantitatively between anisotropic and isotropic fatty substances.

The pathologic process in xanthic tumors of the connective tissue is discussed fully. I believe, with Sick, that the cells of xanthomatous tumors of the tendon sheaths are, like adrenal and some other cells (prostate, corpus luteum), fundamentally metabolically "constituted" in

43. Hammarsten, O., and Hedin, S. G.: Text-Book of Physiological Chemistry ed. 7, New York, Wiley & Sons, 1915, p. 362.

the direction of production of lipids. Perhaps special function and the composition of the synovial fluid (lubrication, degenerated cells) point in this direction for xanthomas of tendon sheaths.

In general, there are numerous analogies between fibrosarcoma and xanthosarcoma, in the relation to trauma, the origin in tendon sheaths and other fibrous structures, slow growth and local malignancy. Distant metastasis of xanthosarcomas appears to be unknown, contrary to recent reports in the literature.

Extensive yellow coloration of sarcomas, particularly of the extremities, may be due (1) to necrosis or pigmentation or (2) to xanthomatous change. Since necrosis and pigmentation are retrogressive processes common to a great variety of neoplasms and do not connote a peculiar and important metabolic addition to the situation as xanthomatosis does, it is recommended that clinical expedience be set aside, and that the term xanthosarcoma be reserved for those cases in which true xanthomatous changes are associated, as evidenced histologically by the presence of xanthoma cells.

While they probably have no bearing on prognosis and treatment, the significance of xanthomatous processes observed in sarcomas should not be forgotten in relation to lipid metabolism in its widest aspect, including cholesterol and its esters. While my patient did not have hypercholesteremia, and the lesion contained comparatively little lipoidal substance, the way is still open to identify some particular order of general systemic fatty disturbance in other cases of xanthoma and (or) xanthosarcoma. It is urged that this be inquired into in future cases of xanthoma and xanthosarcoma. Such inquiries would answer the question whether one is overlooking a general fatty dyscrasia in the xanthomatous patient, which is far more important to his well-being than the tumor which, more or less incidentally, is signaling the information.

Histologic sections are deposited in the Laboratory of Dermatological Research, University of Pennsylvania (D. R. 2275), and at the Army Medical Museum, Washington, D. C. (36477).

INHIBITION OF THE BLADDER

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AND
D. K. ROSE, M.D.
ST. LOUIS

The physiologic basis of many varieties of dysfunction of the bladder is as yet ill understood. Patients present themselves with frequency, urgency or difficulty in urinating for which no adequate explanation is found in the urinary tract. Although it is generally recognized that a lesion of the central nervous system, of the peripheral nerve supply or of the musculature of the bladder can produce dysfunction, the actual cause of symptoms in many patients is frequently overlooked.

In interpreting these symptoms assistance is obtained by studying the activity of the bladder and the sensations experienced by the patient during filling. By using a cystometer with a constant recording mechanism, a graphic representation of the reaction of the bladder to filling is made, and the points at which sensations are experienced can be plotted on the tracing. However, it is well to keep certain effects in mind in interpreting the curves. It is generally recognized that the pressure attained at any volume in the normal bladder will depend on the rate of introduction and also on the temperature and type of fluid used. Temperatures of either extreme and too rapid filling are to be avoided. It is less well recognized, however, that psychologic effects, particularly those resulting in inhibition, may produce curves from a normal bladder which simulate gross pathologic conditions. To obtain a fair idea of the effect of such influences, which operate to a greater or a lesser degree in the making of all cystometrograms, at least two curves should always be made.

It is important also to distinguish between the true contraction of the detrusor urinal muscle and a rise of pressure due to abdominal straining. If the rise is due to the latter cause, it can be sustained only while the breath is held, and when straining is stopped the writing point immediately falls back to the starting level. The contraction of the detrusor muscle, on the other hand, continues in spite of normal breath-

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ing, and even if the reaction is controlled by voluntary inhibition, the writing point descends slowly and in a series of steps.

The observations submitted here are the results of a study of the inhibitory effects on the bladder in certain patients with dysuria. The cystometer, introduced by one of us (Dr. Rose) in 1926, was employed, and the technic previously described was used.[1a]

CYSTOMETROGRAPHIC DATA AND CLINICAL APPLICATION

Curve *A* in chart 1 represents the cystometrogram of a normal subject. The pressure was adapted to the volume smoothly, and the tension rose more rapidly as the limiting volume was reached (indicated by an asterisk), terminating in a spontaneous expulsive reaction. Here the bladder reacted to stretch by a simultaneous coordinate contraction, producing a smooth curve.

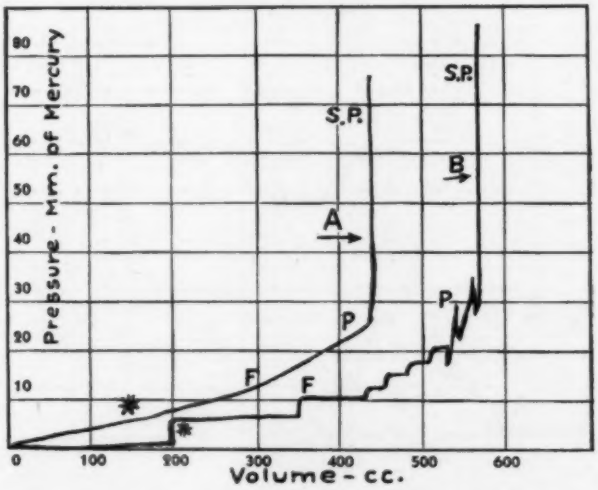

Chart 1.—Cystometrograms of a normal subject. In this and the following charts the asterisk indicates the first desire to void; *F*, fulness; *P*, pain, and *SP* severe pain.

Curve *B* in chart 1 is another tracing made at the same examination. The subject was asked to relax the bladder as much as possible and to try not to void. The curve is flat for 200 cc., at which point there was an abrupt rise of 6 mm. of mercury, which was associated with a slight sensation in the bladder. This rise was immediately inhibited, and filling continued on a plateau of pressure for about 150 cc., when a second rise occurred. This process was repeated with shorter plateaux as the distention proceeded, producing a "step" effect, and it will be noticed that two diphasic waves occurred in the early phase of the emptying contraction of the bladder. In this patient inhibition had the effect of permitting a

1. (*a*) Rose, D. K.: Determination of Bladder Pressure with the Cystometer: A New Principle in Diagnosis, J. A. M. A. **88**:151 (Jan. 15) 1927; Changes in the Wall of the Bladder Secondary to Prostatic Hypertrophy, Arch. Surg. **25**:783 (Oct.) 1932.

greater amount of stretch to take place without an increase in the resistance of the wall of the bladder, but this amount grew progressively less with increasing volume and the resulting tendency for inhibition to be overcome.

These two curves, that produced without attempt at inhibition (*A*) and that produced with an attempt at inhibition (*B*), demonstrate the variability in normal curves as influenced by inhibition. Notably curve *B* should be higher and shorter than curve *A*, but it is lower and longer as a result of inhibition. It is a fact that in the neurogenic bladder of the diminished sensation type the normal relationship is reversed just as is shown in chart 1, often so much that it is unwise to overdistend such a bladder. If the cause of the reversal is inhibition, it is suggested

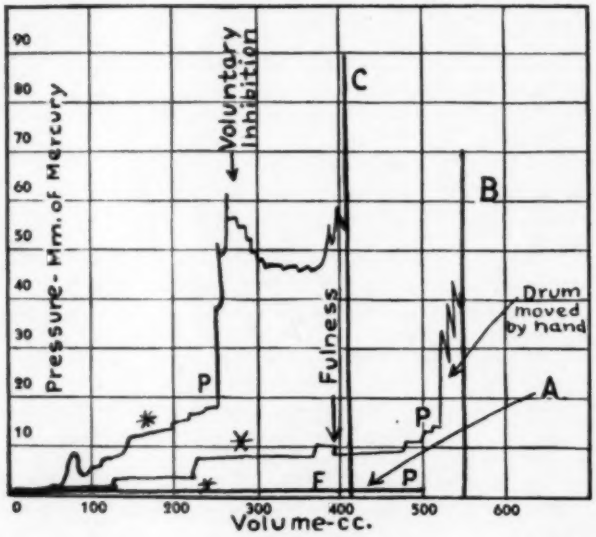

Chart 2.—Cystometrograms of an introspective subject.

at the time by the action of the patient and can be checked by still another cystometrogram, as the repeated filling and emptying of the bladder of normal innervation will decrease capacity and increase intracystic pressure.

Three tracings (chart 2) were made at the same examination of an introspective person who, in addition to being unduly fearful, experienced considerable pain from the catheter due to posterior urethritis. Curve *A* is entirely flat for 500 cc., with no reaction of the detrusor muscle; yet filling was stopped on account of pain caused by overdistention. When curve *B* was made the patient was less frightened, and the pain in the urethra had subsided, probably due to less protective spasm. This curve shows the marked inhibitory phases demonstrated in chart 1. Filling was discontinued when the patient complained of pain (*P*), and an appreciable interval elapsed before he could start an expulsive reaction. This was assisted by contraction of the abdominal wall, which raised the pressure 20 mm. of mercury. As the

bladder went into active contraction, several waves appeared, inaugurating the response of the detrusor muscle, which is represented by the usual uninterrupted vertical line, in this case broken by inhibition which was being rapidly overcome but still showed its effect on the early phase.

Curve *C* shows what is believed to be the true condition, a rather active curve and early expulsive reaction. While the expulsive pressure was still rising, the patient was told to relax the bladder and try not to void. No fluid escaped around the catheter and, in spite of the filling which was continued to maintain a stretch stimulus, the pressure fell off in a series of steps during the introduction of 140 cc. At this point the desire to void overcame the inhibitory effect, and two diphasic waves preceded a typical expulsive reaction.

Such a phenomenon as that demonstrated by curve (*C*) is seen in cases of psychic urinary retention, that is, in cases in which a normal person is unable to void owing to mental distraction, fear, embarrassment, etc.; in cases of some types of postoperative retention; and in cases of urethritis, in which the patient does not void because of the fear of urethral pain. Also, coupled with early prostatic hypertrophy when a small amount of concentrated urine and a low grade urethritis markedly decreases the normally possible force and size of the stream, an inhibition associated with the knowledge and fear of urinary obstruction is a factor in the occasional complete retention which is relieved by a single catheterization.

In this experiment, as the confidence of the patient returned the inhibition was lost. However, the stimulation of the first filling, increasing the tone of the musculature of the wall of the bladder, is a factor to be noted in the increased excitability of the bladder shown in tracing *C*.

These three cystometrograms demonstrate the value of repeating the examination to rule out psychic influence which otherwise could produce a curve that one might think due to incompetence or decompensation of the muscle or to faulty innervation.

Cystometrograms of patients with dysuria were next studied to find out what part inhibition, or the lack of it, played in explaining the symptomology. These, on the basis of the conditions presented by the patients, have been placed in four groups which demonstrate different aspects of this problem:

1. Total transverse lesions of the cord with well established reflex activity.
2. Partial lesions of the cord showing bilateral, incomplete involvement of the pyramidal tract.
3. Cerebral lesions without signs of damage to the pyramidal tract.
4. Local lesions of the bladder, of which there were two types: (*a*) compensating hypertrophy of the wall of the bladder behind an obstruction and (*b*) a local lesion of the bladder without obstruction of the outlet or hypertrophy of the wall.

There were three records in the first group, eight in the second, five in the third and a large number from the urologic clinic in the fourth. An example from each group is given.

Chart 3*A* shows the curve for a patient with a complete traumatic transverse lesion of the cord at the level of the eleventh and twelfth thoracic segments, of three years' duration. Automatic micturition commenced three months after the accident. At the time of examination the bladder showed no infection. It was emptied completely but frequently. (Such a patient does not necessarily carry residual urine, though a small amount is common. A larger amount of residual urine may occur, but it is associated with changes in the wall of the bladder.) Examination showed that all sensations were lost up to the inguinal ligament on both sides. The reflexes in the lower extremities were increased, and clonus and a Babinski sign were present bilaterally. The patient had no sensation of fulness in the bladder except a dull feeling in the lower part of the abdomen and no desire to void. If he allowed the bladder to become over full, it emptied spontaneously without his knowledge, but he had found that he could prevent this accident by rubbing or pulling the penis or by pressure on the lower part of the abdomen in

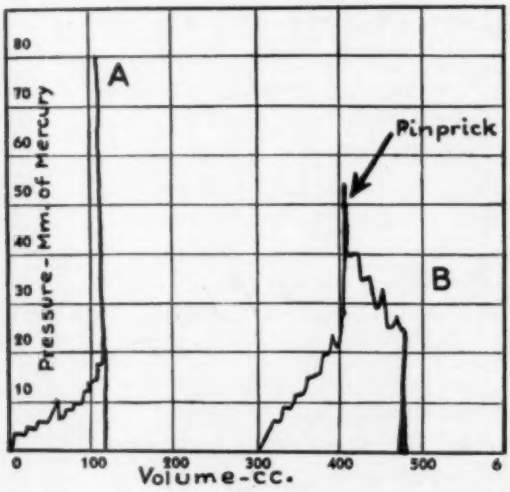

Chart 3.—*A*, cystometrorgram of a patient with a complete traumatic transverse lesion of the spinal cord. *B*, a cystometrogram of the same patient showing the response to a pinprick.

the earlier stage of filling, thus precipitating the reaction at a convenient time. Stimulation of the sole of the foot was also effective in producing an emptying contraction of the bladder.

The curve shows high pressure and low volume, and when the patient was asked to try to relax the bladder no effect was produced. The second curve shows the effect of a sharp pinprick, that is, the effect of a painful type of stimulus to the glans penis during the response of the detrusor muscle, which is seen to subside in a series of steps (drum moved by hand). "Painful" stimulation of the sole of the foot had a similar effect, but no effect was produced from such nociceptive stimulation of the anterior wall of the abdomen.

These two curves show that a bladder released from cerebral control can regain tone and function satisfactorily (with no residual urine or only a small amount) and not require catheterization, which

would cause infection, and that painful stimuli in such a bladder reflexly can inhibit the contraction of the wall when cerebral inhibition is impossible. A comparison of these cystometrograms with those made in a case in which there was no lesion of the spinal cord shows conclusively that the inhibitory reflex center is in the cord and may be stimulated by the cerebrum or peripherally below a complete section of the cord.

The higher percentage of postoperative retention following perineal operations can be explained in part on the basis of cystometrogram *B* in that the first act of urination is a depression of the perineum which

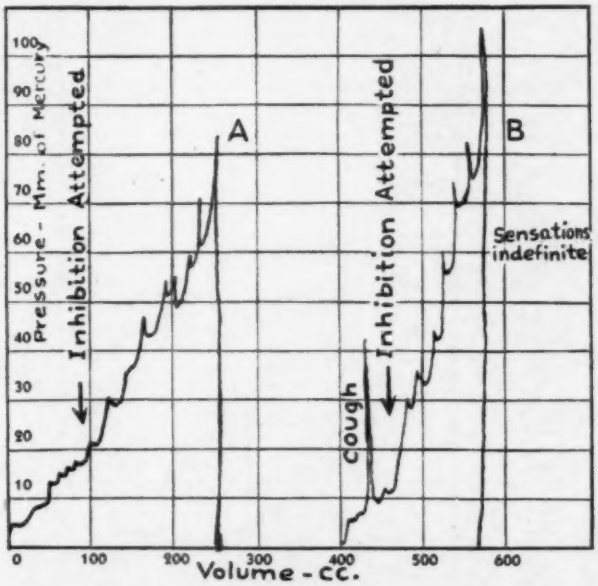

Chart 4.—*A*, cystometrogram of a patient with spasticity and weakness of both lower extremities, some ataxia and complete block of the spinal cord. *B*, cystometrogram of a senile patient with marked arteriosclerosis and impairment in his mental status.

would cause a pain stimulation type of reflex inhibition in a comparable manner to pinprick (curve *B*) and so allow overdistention of the bladder.

Curve *A* on chart 4 is the cystometrogram of a patient who on neurologic examination showed spasticity and weakness of both lower extremities, which were more marked on the left, some ataxia, but no sensory loss, and a complete spinal block to iodized poppy-seed oil 40 per cent. The reflexes were hyperactive on both sides, with clonus and a positive Babinski sign bilaterally. The patient complained of urgency and incontinence of urine for six months, and at operation a fibroblastoma of the spinal meninges extending from the eighth to the tenth dorsal segment was found. The curve shows small volume, high pressure and feeble inhibitory power.

Curve *B* on chart 4 is the cystometrogram of a senile patient who presented evidence of marked arteriosclerosis and general impairment in his mental status. He had frequency, marked symptoms of urgency and enuresis, for which a urologic examination was requested. This revealed no infection and no anatomic variation in the bladder or urethra, but again the curve shows an imperfectly controlled reaction of the bladder to filling.

Release of inhibition demonstrates itself either as frequency and urgency of urination or, in its more exaggerated form, as incontinence,

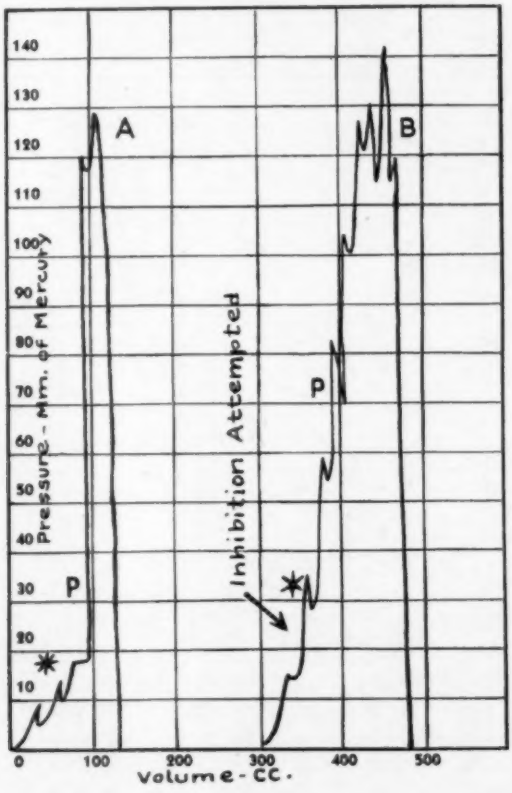

Chart 5.—Cystometrograms of a patient with a Hunner ulcer of the bladder.

varying from a continuous drip to the involuntary expulsion of small amounts of urine. Single curves for two patients, one with spinal block and the other with an inefficient cerebrum, are presented on one chart to point to the similarity of effect on bladder control when inhibition is attempted. In the case of senility (curve *B*), catheterization would prolong the frequency or incontinence by adding local reflex irritability. Such irritation being omitted, the prognosis is good on improvement of cerebration, often adversely influenced by absorption of infection.

The curves for patients with local lesions of the bladder present features identical with those illustrated in the two foregoing groups, that is, a rapidly rising curve with only slight inhibitory phases. Two curves from this group, however, are shown to illustrate special points.

Curves *A* and *B* in chart 5 were made from the same patient, who suffered from a Hunner ulcer of the bladder. Curve *A* shows the typical early and powerful expulsive response, and *B* has been included to show the effect of a maximal inhibitory effort on this response. It will be observed that although inhibition cannot stop the powerful contraction of the bladder, it does produce a modification which is essentially a resolution of this expulsive contraction into a series of diphasic waves of increasing amplitude. That is, the response of the detrusor muscle is represented by a compound of fused diphasic waves. From a clinical standpoint, the result of asking the patient to inhibit while effecting hydraulic distention of such a bladder is graphically portrayed. It assists in increasing the capacity in relation to a contracted, high pressure. In *B*, owing to the stimulation of the filling, *A*, one would expect an immediate higher pressure but associated with a smaller capacity. Filling was discontinued as soon as the expulsive contraction commenced, to avoid effects from this cause.

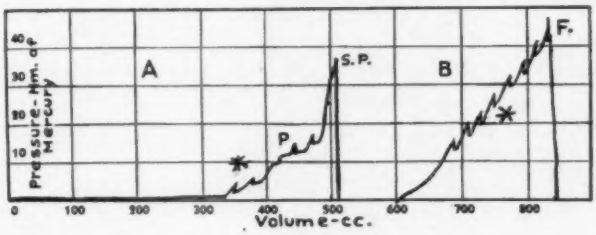

Chart 6.—Cystometrograms of a patient with an enlarged prostate which obstructed the opening of the bladder.

The cystometrograms in chart 6 were made in a case in which the opening of the bladder was obstructed by an enlarged prostate gland and 900 cc. of uninfected urine was retained in the bladder. From the standpoint of inhibition, *A* shows the flat curve and also the steplike ascent. Curve *B* is higher at the onset owing to the stimulation of the first filling and the patient's becoming reassured. It is interesting to note the sensations first desire to void (indicated by an asterisk), pain (*P*) and severe pain (*SP*). The delay of the first desire to void is associated with the flat curve of inhibition and becomes normally placed (at 150 cc.) in curve *B*. This cystometrogram was carried out only sufficiently to determine these motor and sensory points.

These cystometrograms definitely show the desirability of making two curves at the time of the first cystometric examination in that *A* could readily be interpreted as indicating a neurogenic bladder without *B* to correct the sensation readings. The plateau in *A* we associated with some muscular decompensation exhibited by the 900 cc. of uninfected residual urine. Such a normally innervated musculature [1b] always

responds to the stimulation of filling by decreased capacity and high pressure, as is frequently observed in irrigation of the bladder and at cystoscopic examinations in our daily practice.

COMMENT AND SUMMARY

It has been shown that the normal subject can modify the reaction of his bladder at will over a considerable range of filling and that this may take the form of inhibition. The voluntary inhibitory effect is exaggerated in the presence of local pain, and it is further shown that a painful stimulus applied to somatic areas closely related to the sacral segments will produce inhibition of the bladder in a patient with a transverse lesion low in the spinal cord.

Voluntary inhibition is completely absent in a person with a transverse lesion of the spinal cord, and it is reduced in a subject whose main neurologic symptoms indicate partial damage of the pyramidal tract. It would appear, therefore, that descending pathways mediating inhibitory influences have also been damaged. Since voluntary inhibition is abolished in a person with a lesion as low as the eleventh or twelfth thoracic segment, the final pathway for this effect must be through nerves leaving the cord below that level and not through the hypogastric nerves. This is supported by the observation that reflex inhibition has a focal point of stimulation representing this area of the cord and that stimulation of areas more closely related to the hypogastric nerves has no such effect.

Inhibitory power is reduced in certain cerebral lesions, and here the interference would appear to be with centers originating the inhibitor impulses. Impairment of control in a person with a local lesion of the bladder is regarded as an "escape" phenomenon; that is, the irritability of the bladder mechanism overcomes the inhibitory control.

The bladder in the stage of reflex activity following total section of the cord above the sacral segments differs from the normal bladder only in the absence of sensation and in the lower volume it will tolerate; otherwise the mechanism is entirely coordinate and adequate. The contraction of the detrusor muscle always precedes relaxation of the sphincter muscle, as shown by the high pressure attained before fluid begins to escape. In order that the bladder may empty completely, the sphincter muscle remains relaxed until the end of the contraction of the bladder. Relaxation of the sphincter muscle is therefore not the primary event in micturition but appears rather to be dependent on and conditioned by the expulsive contraction of the detrusor muscle.

Voluntary inhibition was invoked to study the response of the detrusor muscle, and it was found that under this influence it undergoes a resolution into a series of diphasic waves showing a tendency to fuse.

Similar waves were often observed to precede the expulsive reaction and appear to be due to transient inhibition of its early phase. This observation supports the view that the response of the detrusor muscle is a motor tetanus and therefore is produced by an increase in the number of efferent volleys of nerve impulses impinging on the muscle in a given interval of time.

In view of the marked acceleration of the curves in certain of the conditions demonstrated in this paper, it would appear that the filling of the normal bladder depends on a graded inhibition of a tendency which the bladder possesses to go into early and active contraction. Evidence has already been presented by Denny-Brown and Robertson [2] that the contraction of the detrusor muscle is due to a process of wave summation and also that inhibiting influences operate at the sacral level. Our observations support this view. It is clear also that a pathway through the hindbrain is not essential for the emergence of an expulsive reaction, though such a "long circuit" pathway may exist in the intact animal as an additional means of facilitating higher control and coordination of the bladder.

It seems reasonable now to suggest that the reflex mechanism in the sacral portion of the cord operates in the following manner: As distention proceeds, the progressive stretch of the wall of the bladder elicits a progressively increasing number of afferent impulses. These pass back to the cord and, in the absence of a "blocking" effect, immediately spread over to the efferent side and soon build up a tetanic level of stimulation which produces an expulsive reaction. The function of inhibition is to regulate this mechanism according to the needs of the patient by imposing a variable block between these two pathways.

Learmonth [3] put forward the view that the contraction of the detrusor muscle and the relaxation of the involuntary sphincter muscle are carried out by separate nerves, and he described the hypogastric nerve as a "filling" nerve and the pelvic nerve as an "emptying" nerve. This carries with it the assumption that the anatomic division into sympathetic and parasympathetic systems coincides with mutually exclusive physiologic functions. That this is not so in other parts of the body in animals has been shown by many observers (Dale and Gaddum,[4] Heinbecker [5] and others) and in relation to the bladder by MacDonald and McCrea.[6] Furthermore, clinical experience lends little support to the

2. Denny-Brown, D., and Robertson, G.: Brain **50**:149 and 397, 1933.

3. Learmonth, J.: Tr. Med.-Chir. Soc. Edinburgh, 1931-1932, p. 43; in Edinburgh M. J., April 1932.

4. Dale, H., and Gaddum, J. H.: J. Physiol. **70**:109, 1930.

5. Heinbecker, P.: Personal communication to the authors.

6. MacDonald, A. D., and McCrea, E. D. A.: Quart. J. Exper. Physiol. **20**:379, 1930; Brit. J. Urol. **6**:119, 1934.

theory of equal and opposite functions for the so-called "presacral" and "pelvic" nerves.

Since Eccles'[7] work on the selective action of the superior cervical sympathetic ganglion cells, showing that the same preganglionic stimulation produces effects both of facilitation and of inhibition in different groups of postganglionic fibers, another explanation seems possible. According to this theory, the preganglionic discharge set up reflexly by filling the bladder would be differentiated by the cells of the pelvic ganglion, inhibitory impulses being set up in some postganglionic fibers and excitator impulses in others, these passing respectively to the sphincter and the detrusor muscle. Such a mechanism would be more convincing in explaining the dependence of the relaxation of the sphincter muscle on the activity of the detrusor muscle.

It is further pointed out here that the involuntary activity of the bladder is only relative in the normal subject and that "willed" control of this "involuntary" system is exerted through the power of inhibition.

7. Eccles, J. C.: J. Physiol. **85**:209, 1935.

EFFECT OF ANESTHETICS ON LYMPHATIC ABSORPTION FROM THE PERITONEAL CAVITY IN PERITONITIS

AN EXPERIMENTAL STUDY

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One of the most important, if not the principal, factor in peritonitis is the accompanying toxemia. Since the success or failure of treatment depends largely on measures designed either to neutralize the toxins as formed or to prevent their absorption into the systemic circulation, it is natural that a great deal of interest has been evinced in the manner in which these toxins enter the systemic circulation.

A survey of the literature reveals that the absorption from the peritoneal cavity is as yet not thoroughly understood. There are many factors which affect the rate of absorption, and there is more than one avenue of escape of material from the peritoneal cavity. While it is not the purpose of this report to comment on how material, whether it is particulate, crystalloid or a colloid solution, leaves the peritoneal cavity, a brief summary of the evidence at hand may be of interest.

The first study on peritoneal absorption is generally credited to von Recklinghausen [1] in 1863. Using silver nitrate stains, he stated that particulate material entered the lymphatics through definite openings, or "stomas," between the endothelial cells. This view was generally accepted until MacCallum [2] in 1903, by means of painstaking work, disproved the presence of these "stomas" and concluded that particulate material passed directly through the living cytoplasm of the endothelium. He also expressed the belief that respiratory movements were an important factor in promoting this absorption.

This view has since been supported by other physiologists, especially Cunningham,[3] who made a number of contributions to the literature on this subject and in 1926 summarized his views, together with a survey of the literature published up to that time. He agreed with

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1. von Recklinghausen, F. I.: Virchows Arch. f. path. Anat. **26**:172, 1863.

2. MacCallum, W. G.: Anat. Anz. **23**:157, 1903; Bull. Johns Hopkins Hosp. **14**:105, 1903.

3. Cunningham, R. S.: Physiol. Rev. **6**:242, 1926.

MacCallum that particulate material passes directly through the cells, and by an ingenious study of absorption in fetuses he showed that respiratory movements were the predominant factor.

It is the consensus among contributors to this subject that the diaphragmatic peritoneum plays the only significant rôle in the removal by the lymphatics of particulate material from the peritoneal cavity and that the mediastinal lymph nodes serve to collect the lymph draining from the peritoneal cavity. Crystalloids and colloids are almost wholly taken up by the venules of the omentum.

Buxton and Torrey [4] in 1906 injected nucleated erythrocytes and suspensions of living bacteria into the peritoneal cavity and timed their appearance in the blood and lymph streams.

In 1914 and 1915 Dandy and Rowntree [5] studied the absorption of phenolsulfonphthalein from the peritoneal cavity. They found that it appeared in the blood stream in from two to four minutes, in the urine in from four to six minutes and in the lymph stream (thoracic duct) in from twenty to fifty minutes. They also studied the effect of posture on drainage and discovered that the rate and amount of absorption was about equal in all postures except pelvis down (Fowler position), in which position the absorption was uniformly about 15 per cent less. They summed up the literature on absorption from the peritoneal cavity that had been published up to that time and concluded that the lymphatic absorption of fluids was greatly overestimated, that most of the absorption takes place through the blood stream and that this holds true for both bacteria and toxins. All their studies were made on normal animals, i. e., in the absence of peritonitis.

In 1925 Steinberg,[6] in a study of absorption from the peritoneal cavity in dogs, stated that drainage of the thoracic duct has no value in the treatment of peritonitis. In 1927 Drinker and Churchill,[7] wishing to make intravital studies of the capillaries, tried a great many kinds of dyes, inks and colloidal graphite solutions and found that hydrokollag 300, a graphite base for printer's ink, when neutralized and diluted with a saline-acacia solution, gave the best results. Many of the particles are smaller than erythrocytes, and there is no tendency to plug the lymphatics by clumping, as other inks do, or to diffuse out into the perilymphatic tissue spaces, an annoying feature of the soluble dyes.

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4. Buxton, B. H., and Torrey, J. C.: J. M. Research **15**:55, 1906.

5. Dandy, W. S., and Rowntree, L. G.: Beitr. z. klin. Chir. **87**:539, 1915; Ann. Surg. **59**:587, 1914.

6. Steinberg, B.: J. Exper. Med. **42**:83, 1935.

7. Drinker, C. K., and Churchill, F. D.: Proc. Roy. Soc., London, s.B **101**: 462, 1927.

Florey in 1927 [8] used hydrokollag 300 and declared it to be far superior to many other substances which he had used. As a result of his experiments, he concluded that intra-abdominal pressure, as affected by the activity of the animal and by the rate and depth of respiration, plays a big rôle in the removal of particulate material from the peritoneal cavity. He also made the suggestive remark that experiments performed on the relative rates of absorption through the lymphatics in anesthetized animals give a far from accurate picture of what really happens in the normal animal.

In 1927 Higgins,[9] wishing to study the absorption of particulate material from the peritoneal cavity of dogs, discovered that nothing definite was known of the lymphatic system of the dog. Using hydrokollag 300, he worked out the lymphatic routes draining the peritoneal cavity in these animals. He found five routes through which particulate material may be removed: (1) the sternal route—the most important—which traverses the substernal aerolar tissue and empties into the lymph nodes between the first and the second rib and thence into the thoracic duct or the right lymphatic duct just at or before the venous confluence; (2) the pulmonary route, consisting of lymphatics and nodes in the anterior mediastinum and bronchial nodes at the base of the lungs; (3) the thoracic duct itself; (4) the retroperitoneal route, and (5) the direct peritoneal route. The sternal route transmits about four fifths of the entire amount of the particulate material. He then studied the rate of absorption of this material; this phase of his work will be referred to later. Other investigators, meanwhile, were studying the subject from other points of view.

Brown in 1927 [10] reported experimental work in dogs and cats which seemed to show that lymphatic drainage of the diaphragm is only subsidiary to the removal of the material by the venules of the omentum and mesentery. He expressed the belief that lymphaticostomy, which had been advocated as a method of preventing toxins from entering the circulation, was of no value in spreading peritonitis. Similar findings were reported by Poynter,[11] who felt that the venules of the omentum were the chief avenue of exit of toxic material from the peritoneal cavity, although he admitted that of the lymphatic drainage, the diaphragmatic route is the only one of any consequence.

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8. Florey, Howard: Brit. J. Exper. Path. **8**:479, 1927.

9. Higgins, G. M., and Graham, R. S.: Lymphatic Drainage from the Peritoneal Cavity in the Dog, Arch. Surg. **19**:453 (Sept.) 1929.

10. Brown, K. P.: Brit. J. Surg. **15**:528, 1927.

11. Poynter, C. W. M.: Proc. Staff Meet., Mayo Clin. **2**:263, 1927.

David in 1927 [12] and David and Sparks in 1928 [13] experimented with injections of Bacillus coli into the peritoneal cavity. They found that bacteria were absorbed into the blood stream and lymphatics at practically an equal rate, that plastic exudate cuts down the rate and amount of absorption and that when the exudate is well developed absorption into the blood stream or lymphatics practically ceases. However, the presence of a transudate induced by hypertonic dextrose solution injected into the peritoneal cavity causes rapid absorption into both blood stream and lymphatics. This last statement bears out the clinical observation that so-called "wet" types are subject to a higher mortality than "dry" types of spreading peritonitis.

In summarizing all these conflicting statements several points are obvious:

1. Observations which are carried out on normal peritoneum have little value in helping one to estimate the rate and amount of absorption of toxic material from an abdomen which is the seat of a spreading peritonitis.

2. Prior to Higgins' [14] fine work on dogs, experimental studies in these animals on the lymphatic drainage from the abdomen with regard to the efficacy of lymphaticostomy are of little or no value because the thoracic duct plays such a minor rôle.

3. There is a difference in the behavior of crystalloids as compared with that of particulate material in that they are removed with equal facility by both the blood and the lymph streams.

4. Although Florey pointed the way with his experiments, practically none of the other investigators considered the effects of diaphragmatic activity on the rate of absorption of toxic material from the peritoneal cavity until Higgins followed up this suggestion in 1929.

Using ether exclusively, Higgins found that the graphite appeared in the lymphatics in approximately three minutes. After phrenicectomy, he found that it required from eight to fifteen minutes. Also, if the abdomen were opened and the omentum excised, or if the intestines were merely handled and then replaced, the appearance of the graphite was delayed likewise to from eight to fifteen minutes. However, if the omentum was excised and several days allowed to elapse before the graphite experiment was performed, the rate of absorption returned to normal. He also found that it took from thirty to forty minutes for graphite to appear in the thoracic duct and that after phrenicectomy the appearance in the duct was delayed from one and a half to three hours.

12. David, V. C.: Surg., Gynec. & Obst. **45**:287, 1927.

13. David, V. C., and Sparks, J. P.: Am. Surg. **88**:672, 1928; Tr. Am. S. A. **46**:362, 1928.

14. Higgins, G. M., and Murphy, G. T.: Anat. Rec. **40**:15, 1928.

Since many patients with spreading peritonitis complicating acute perforative appendicitis are operated on, either inadvertently or designedly, during the early stages of the disease, I wished to ascertain, if possible, what effect was exerted by the anesthetic on the rate of lymphatic absorption.

EXPERIMENTAL WORK

To this end a series of animals was first studied to determine the rate of absorption of particulate material (graphite) from the normal abdomen. The

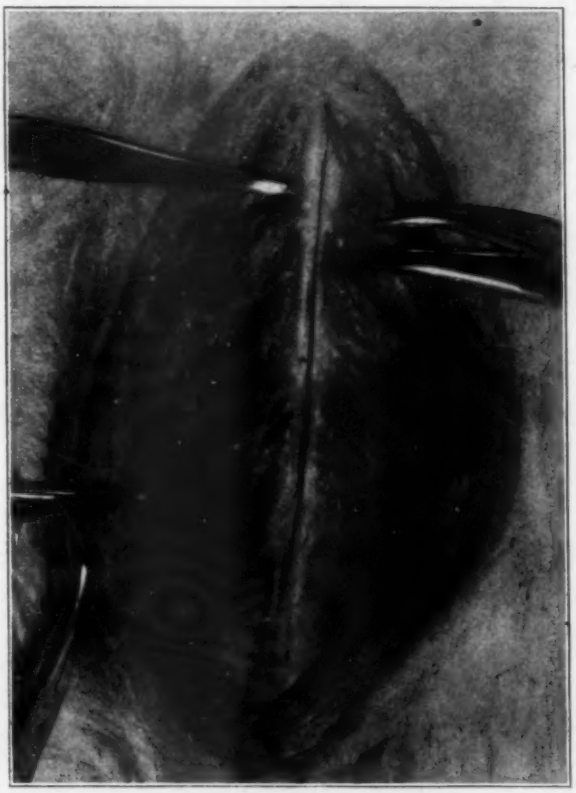

Fig. 1.—Incision in the chest showing the periosteum incised and partially sawed through. About two-thirds actual size.

method devised by Higgins was followed without any difficulty. The animal did not receive any breakfast the day of operation. It was fastened to the operating table, and the chest and abdomen were shaved. The chest was opened in the median line, the periosteum was split in the midline and the sternum was sawed through from the first chondrosternal joint down to the fourth rib, care being taken not to saw through the inferior layer of the periosteum, which was incised with a knife. This exposed the substernal alveolar tissue, which contains the sternal lymphatics, nodes and blood vessels. If one carefully stays in the midline there is

little danger that the dura will be punctured in the procedure. From 8 to 10 cc. of graphite was then injected into the free peritoneal cavity, and the time of injection was noted. The animal was watched until the graphite appeared in the substernal nodes and lymphatics, when the time of appearance was noted.

The graphite used was prepared as follows (Higgins and Murphy's modification of Drinker and Churchill's original method):

Hydrokollag 300 is a colloidal preparation of graphite containing ammonia and a small amount of cherry gum as a protective colloid. It mixes freely with blood serum and acacia without agglutinating. When received, it is a thick syrup with

Fig. 2.—Incision in the chest showing the sternum split and the mastoid retractor separating the halves, exposing the substernal areolar tissue. About two-thirds actual size.

a sediment at the bottom. In preparing it for use it is first shaken and thoroughly stirred up. One hundred and twenty grams is weighed out, and 2 cc. of saturated solution of sodium hydroxide in 250 cc. of distilled water is added. This mixture is then placed high over a Bunsen flame and heated gently while a stream of air is bubbled through it. This procedure, which drives off the ammonia, requires about four hours. The mixture is then diluted with an equal quantity of a saline-acacia mixture (12 per cent acacia in a 1.8 per cent solution of sodium chloride). The entire mixture is centrifugated at moderate speed for ten minutes. The upper

four fifths of the solution is pipetted off into a clean sterile flask, and the remaining liquid is pipetted into a second flask. The cake in the bottom of the tube is discarded. The contents of the second flask are recentrifugated for ten minutes, and the upper four-fifths is again removed and added to the first flask. This process is repeated until practically all the liquid is recovered, the remainder being discarded. All the large particles and lumps are removed by this method. This mixture will keep in the refrigerator for from two to three months.

A total of fifty-nine dogs were used in these experiments. Of these, eleven died during the course of the experiments, either from accidentally rupturing the

Fig. 3.—A substernal lymph node is shown at *x*, filled with graphite. About one and two-thirds actual size.

pleura or from an overdose of anesthesia; in two animals the graphite was injected into the falciform ligament; in one, it was injected into the urinary bladder, and in one, the graphite was discharged into the lumen of the intestine. These were discarded, leaving forty-six animals available for study.

The effect of the anesthetic on the rate of lymphatic absorption from a normal peritoneal cavity was first studied briefly. These results are shown in table 1, and the results under ether anesthesia agree closely with those of Higgins, who used ether exclusively in all his experiments. The slightly longer times of appearance in my experiments (from five to seven minutes) compared with his (from three

to five minutes) may be due to waiting until the lymphatics were well filled and definitely demonstrable.

While the number of animals is admittedly too small to establish sound averages, the figures in table 1 serve to show that the most marked effect on the rate of absorption is produced by the anesthetic which most pronouncedly stimulates the activity of the diaphragm.

After it was felt that sufficient work had been done to establish the fact that anesthetics definitely affected the rate of absorption into the lymphatic system draining the peritoneal cavity, the next step was to observe whether these effects were

Fig. 4.—The normal abdomen injected with graphite, a great deal of which is in the omentum.

the same, in general, when the peritoneum was the site of an inflammatory process. To this end, peritonitis was induced in a large number of dogs, and the graphite absorption experiments were carried out at different periods of duration of peritonitis.

Peritonitis was induced as follows: Under strict aseptic technic the abdomen was opened through a right rectus incision, and the cecum was located. (Strictly speaking, the dog has no appendix, but the distal one third of the cecum is mobile, free and completely peritonized. This serves admirably as an "appendix" for experimental work.) The blood supply to the distal portion was divided between

clamps and tied off. A ligature was placed about the base of the free distal end and tied as tighty as possible. The intestines were then replaced, and the abdomen was closed in layers. The animals were subjected to graphite absorption studies at intervals of twenty-four hours following this. If local peritonitis was desired, nothing further was required. For the successful induction of a spreading peritonitis, immediately after operation the animal was given 1 ounce (30 cc.) of either castor oil or a saturated solution of magnesium sulfate. In practically all the animals which received a laxative, spreading peritonitis developed. In the absence of a laxative, merely a localized abscess developed in most of the animals.

Fig. 5.—Local peritonitis. The omentum is drawn up to the right. The graphite is mainly in the omentum, *x*.

All the animals studied were killed at the conclusion of the graphite experiment, and the abdomen was opened to verify the type of peritonitis.

Seven dogs were studied in which local peritonitis had developed. At different intervals of twenty-four hours after the operative induction of peritonitis, the graphite absorption experiments were carried out. The results are shown in table 2. This study reveals two significant facts: First, the inflammation of the peritoneum brought about a delay in the absorption time, as compared with the absorption time of the normal abdomen, and, second, the anesthetics still stand in the same ratio to each other as they do in the normal animal.

TABLE 1.—*Effect of Anesthetic on the Rate of Lymphatic Absorption from a Normal Peritoneal Cavity*

Anesthetic	Time of Appearance, Min.	Average Time of Appearance, Min.
Ether	7, 5, 7	6.3
Spinal: procaine hydrochloride (80-120 mg.)	13, 12, 15	13.3
Local (for incision in chest)	No graphite in 2 hr.	
Procaine hydrochloride (1%)	No graphite in 2 hr.	0 under 2 hr.
Sodium amytal (35 mg. per Kg. of body weight intraperitoneally	38, 50, 23	37.0

TABLE 2.—*Results of Graphite Absorption Tests on Dogs with Local Peritonitis* *

Duration of Peritonitis After Ligation of Appendix, Hr.	Time of Appearance of Graphite, Min.	Average Time, Min.
24	11.0, 9.5	10.0
48	20.0	20.0
72	30.0, 22.0	26.0
96	36.0, 45.0	40.5

* Ether anesthesia was used.

TABLE 3.—*Results of Graphite Absorption Tests on Dogs with Spreading Peritonitis of Twenty-Four Hours' Duration*

Anesthetic	Time of Appearance of Graphite, Min.	Average Time, Min.
Ether	14, 17.5, 28, 30, 25	22.9
Spinal: procaine hydrochloride (80 mg.)	35, 25, 31, 25	29.0
Sodium amytal (35 mg. per Kg. of body weight intraperitoneally)	35, 45, 45, 45	42.5

TABLE 4.—*Results of Graphite Absorption Tests on Dogs with Spreading Peritonitis of Twenty-Four Hours' Duration*

Anesthetic	Time of Appearance of Graphite, Min.	Average Time, Min.
Ether	20, 19, 17, 24, 37, 27	24
Spinal: procaine hydrochloride (80 mg.)	40, 43, 37, 35 None after 90 min.	49
Sodium amytal (35 mg. per Kg. of body weight intraperitoneally)	48, 88 None after 90 min.	75
Spreading Peritonitis of 96 Hours' Duration		
Ether	46	

Fig. 6.—Anterior wall of the chest reflected lateral so as to be viewed from behind. *X* shows the substernal lymph nodes filled with graphite.

Fig. 7.—Same as figure 6 in another animal.

In preparing animals with spreading peritonitis for study it was found that most of the dogs which were not treated died on the third day, being found dead in the morning or practically moribund, so that it was felt any experimental work would be worthless, even should the animal survive the anesthetic. As soon as this was discovered, attempts to obtain a series of animals with spreading peritonitis of seventy-two hours' duration were abandoned, and for the remainder of the experiment no animal was held more than forty-eight hours after the induction of peritonitis before carrying out graphite absorption studies. One animal, however, survived, and the result is recorded here.

Fig. 8.—Same as figure 6, except that the lymph nodes contain no graphite.

There were thirteen dogs in the group with spreading peritonitis of twenty-four hours' duration. The results of this study are given in table 3. It is seen that the increase in the extent and severity of the inflammatory process has considerably slowed the rate of absorption as compared with the group of dogs with local peritonitis. The anesthetics, however, maintain their relative positions. In the group with spreading peritonitis of forty-eight hours' duration there were fourteen animals available for study. These results are recorded in table 4.

One animal survived for four days and was studied at that time, under ether anesthesia. The result in this animal is shown at the bottom of table 4.

COMMENT

In evaluating the results of this study, there are a number of factors to consider.

First, it is apparent to even the casual observer that the presence of peritonitis cuts down the rate of absorption materially. However, the lymphatics still do pick up material, even in the presence of a virulent well developed spreading peritonitis.

Second, the influence of peristalsis has to be considered. It is well known that spinal anesthesia stimulates peristalsis, and it has been shown that this will stimulate absorption through the lymphatics. However, my personal opinion is that clinically this is of little moment, for as Higgins and others have pointed out, the mere handling of the intestines and the "cold air shock" incident to opening the peritoneal cavity will inhibit peristalsis for a number of hours, counteracting the stimulation from spinal anesthesia.

Third, and what seems to be the most important factor, is the effect of diaphragmatic activity. The effect exerted by the anesthetics on absorption from the peritoneal cavity seems to vary exactly with, and to be dependent on, their activity in stimulating deep and rapid respiration. This is especially true of the inhalation anesthetics. In the experimental work reported here, ether was selected as the most representative, as well as the most widely used, of the inhalation anesthetics, and it practically constantly exerted a greater effect on lymphatic absorption from the peritoneal cavity than the other anesthetics, even though in this study the peristalsis-stimulating effect of spinal anesthesia was not neutralized, the abdomen not being opened or the contents manipulated.

Sodium amytal was used because of its well known depressing effect on the respiration when given in full doses and because of its widespread use in experimental laboratories. It is decidedly not intended to recommend it for use in case of peritonitis, as it is too toxic. However, it points the argument that the rate and depth of excursions of the diaphragm play the greatest rôle in affecting lymphatic absorption from the peritoneal cavity.

From the clinical standpoint, it seems evident that local infiltration anesthesia or regional block anesthesia with 1 per cent procaine hydrochloride or low spinal anesthesia with procaine hydrochloride is superior to the inhalation anesthetics from the standpoint of preventing the large influx of toxins into the systemic circulation that invariably results from the use of an inhalation anesthetic. The acute rise in temperature seen after operation on an abdomen which is the seat of an inflammatory process is a familiar observation, and it seems possible that a considerable portion of this postoperative reaction is due to absorption stimulated by the anesthetic.

SUMMARY

A study is presented of the effect of different anesthetics on the absorption of particulate material from the peritoneal cavity of experimental animals, by way of the lymphatics, in (*a*) normal animals, (*b*) animals with local peritonitis, (*c*) animals with spreading peritonitis of twenty-four hours' duration and (*d*) animals with spreading peritonitis of forty-eight hours' duration.

The results of this study show that in normal animals and those with either local or spreading peritonitis the greatest stimulation to lymphatic absorption (and so to toxic absorption) is produced by the anesthetics which most stimulated the activity of the diaphragm. It is believed, therefore, that local infiltration or regional block anesthesia with 1 per cent procaine hydrochloride or low spinal anesthesia with procaine hydrochloride is the method of choice for operations in the presence of peritonitis.

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ENCEPHALOGRAPHY WITH ANESTHETIC GASES

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The experimental background for encephalography with the use of anesthetic gases has been reported in previous articles.[1] The characteristics of the severe and prolonged reaction following the injection of air and the attempts of various workers to find a suitable substitute were discussed. The use of oxygen by Jüngling [2] in 1922, by Denk [3] in 1923 and more recently in Penfield's clinic,[4] as well as the trial of carbon dioxide, nitrogen and helium by Liberson,[5] were mentioned. A review of the literature on the experimental trial of various opaque fluids was also presented. A theoretical consideration of the various factors involved in the problem of encephalography led to the establishment of certain criteria. In this connection it occurred to me that an anesthetic gas might approximate the ideal desired. In brief, it seemed possible that even potent anesthetic gases might prove safe, since only a limited amount of gas may be injected, and this would be relatively inert except as absorbed. Any sedative or narcotic effect would be secondary to its absorption and concentration in the central nervous system. The handling of the gas and the roentgenographic results would be comparable to those achieved by the use of air. The duration of the presence of the anesthetic gas would depend on such factors as its rate of diffusion and solubility in the cerebrospinal fluid and lipoids of the brain. To investigate these possibilities a method was devised for testing various gases by injection into dogs, air being used as a standard of comparison. Eight anesthetic gases as well as oxygen were studied

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This work was carried out in the service of Dr. Howard C. Naffziger at the University of California Hospital.

1. Aird, R. B.: (*a*) Experimental Encephalography with Anesthetic Gases, Proc. Soc. Exper. Biol. & Med. **31**:715-717, 1934; (*b*) Arch. Surg. **32**:193-217 (Feb.) 1936.

2. Jüngling, O.: Roentgenography of Cerebral Ventricles, Zentralbl. f. Chir. **49**:835-836, 1922.

3. Denk, W.: Ueber Encephalographie und ihre Ergebnisse, Ztschr. f. ärztl. Fortbild. **20**:426-430, 1923.

4. Cone, W.: Personal communication to the author.

5. Liberson, F.: Use of Various Gases in Encephalography: Summary of Two Hundred and Ten Cases Using Simultaneous Displacement Apparatus, Am. J. M. Sc. **185**:478-484, 1933.

in this manner. Of this group, nitrous oxide and ethylene seemed promising. Their injection appeared entirely safe, their narcotic effect was slight but definite, good roentgenographic results were obtained, irritative effects were minimal and no untoward after-effects were observed. Special control studies were then made. No neuropathologic changes were found in the brain, cord or meninges after repeated injections of these gases. Cytologic and pressure studies were made on the spinal fluid after injection, and the results were found to be essentially comparable to those obtained with air. The conclusion was reached that nitrous oxide and ethylene were safe and that their trial in man was justified. The present report presents the results obtained with these gases in encephalography on human beings.[6]

METHODS

Technic of Injections.—The method and technic of encephalography adopted for this study were essentially the same as those previously used in this clinic with air.[7] The method had proved satisfactory, and it was felt that a fairer comparison of the gases could be made if the same method were used. This method consisted of a simultaneous drainage of cerebrospinal fluid and its replacement with gas by means of two spinal punctures in the lumbar interspaces. The gas was injected slowly and at constant pressure (approximately the initial pressure) through the upper needle. A Boulitte manometer, connected by tubing to the injecting syringe and needle, was used to control the pressure of injection. The cerebrospinal fluid drained freely during the procedure from the lower needle. The injections were done with the patient in the sitting position and under anesthesia. Tribromethanol in amylene hydrate and procaine hydrochloride locally were used for adults, while the induction of anesthesia with ether proved adequate for children. As complete an exchange of gas and fluid as possible was effected in all instances.

The only modification of this technic for the anesthetic gases was the use of a closed injection system to prevent the escape or dilution of the gas to be injected. This closed system consisted of a rubber bag as a reservoir for the anesthetic gases, connected to the syringe and tubing by means of a three way petcock (fig. 1). Turning of the petcock allowed in turn for the filling of the syringe from the bag and then the injection of the contents of the syringe under controlled conditions of pressure and volume measurement through the upper needle, the manometer being connected to the injection system as already mentioned. Small rubber tubing with adaptors for connecting the needle and the petcock, a T or Y glass tube for the side connection to the manometer and a rubber bag with a three way petcock

6. Both nitrous oxide and ethylene have been tried in ventriculography. Although the results were satisfactory, studies along this line have not been continued. Since ventriculography is ordinarily tolerated better than encephalography and the air may be removed if it does cause a severe reaction, and also since ventriculography is usually reserved for cases in which operative intervention quickly follows, the use of the anesthetic gases has not the same advantages in this procedure as in encephalography.

7. Stone, Robert S., and Jones, O. W., Jr.: Encephalography: A Review of One Hundred and Thirteen Cases, and a Report of Post-Mortem Studies on the Injection of Air, Radiology **21**:411-419, 1933.

connected, as shown in figure 1, constitute the necessary equipment. An additional rubber tube with a small piece of cotton packed and fixed inside the tubing as a bacterial filter suffices to connect the tank and bag for filling purposes. The rubber equipment should be boiled in water for at least three minutes before it is used and should be conveniently wrapped separately in a sterile towel.

Roentgenologic Technic.—After the injection of gas the patient was placed on his back and transferred in this position to the x-ray table. Anteroposterior and horizontal transverse views were taken for visualization of the anterior horns, and the films were immediately examined to determine whether or not adequate filling had been obtained. If the injection merited continuation of the roentgen series, the patient was turned so that, successively, the other three sides of the head (occiput and right and left sides) were uppermost. Thus, even though the filling was not complete, each portion of the ventricular system was filled with the gas. Two roentgenograms were taken in each position; one was a vertical projection

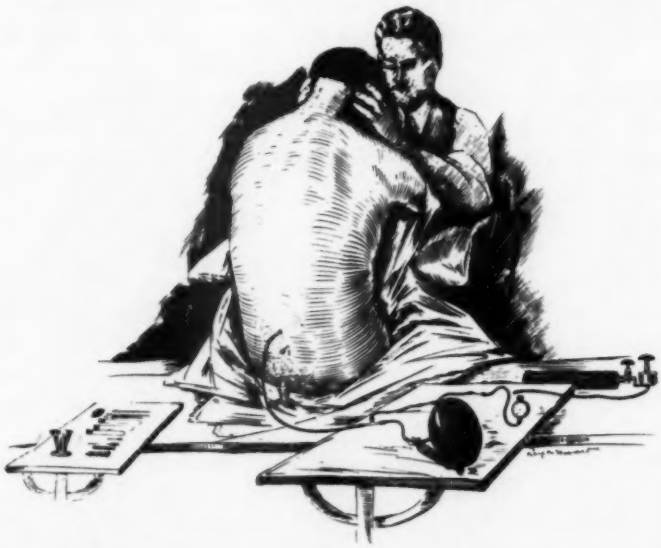

Fig. 1.—Sketch illustrating the setup and method of closed system of encephalographic injection of anesthetic gases.

made with the x-ray tube above the patient's head, with the aid of the Potter-Bucky diaphragm, and the second, a horizontal-transverse projection made with the tube at the side of the patient's head, with the aid of a portable Lysholm grid. In this fashion visualization of each portion of the ventricular system is possible in two different planes. Such "geometrical" views have been found to have a distinct advantage in the localization of any positive roentgenographic findings.[8] The sequence of taking the films was occasionally varied, and ordinarily the region under suspicion was studied first (after the two initial projections with the occiput down) in order to take advantage of all the gas possible.

8. Naffziger, Howard C.: Personal communication to the author. Stone and Jones.[7]

A satisfactory routine which involves a minimum of turning the patient and changing the position of the x-ray tube is as follows (with the patient lying down):

A. Occiput down (for visualization of the anterior horns and third ventricle)
   1. Anteroposterior projection
   2. Horizontal transverse projection

B. Brow down (for visualization of the occipital horns)
   3. Horizontal transverse projection
   4. Postero-anterior projection

C. One side of the head down—the side opposite to that under suspicion, as determined clinically or by study of the first two views—(for visualization of the temporal horn and the body of the uppermost lateral ventricle)
   5. Vertical lateral projection
   6. Horizontal anteroposterior or postero-anterior projection

D. Other side down (for visualization of the other temporal horn and lateral ventricle)
   7. Horizontal postero-anterior or anteroposterior projection
   8. Vertical lateral projection

E. Repeat or special views, as determined by study of the wet films previously taken

Bacteriologic Control Studies.—Nitrous oxide and ethylene from anesthetic tanks were run through a sterilized system of tubing, petcock and needle similar to that used in the encephalographic procedure, and each gas was bubbled into flasks of broth for ten seconds and one minute, respectively. One hundred cubic centimeters of air was likewise bubbled through broth, a sterile Luer syringe being used to force it through the sterilized encephalographic equipment as before. Subsequent plating and the original broths failed to show growth in four days of incubation.

In spite of these negative results, as an extra precaution a small cotton plug was inserted into the tubing used for filling the bladder. Thus a bacteriologic filter was provided which was sterilized with the tubing for each procedure.

ENCEPHALOGRAPHY WITH AIR AS A STANDARD OF COMPARISON

To evaluate properly the results obtained with the anesthetic gases in this study, it seemed essential to know the comparative results obtained with air, the method of injection being fundamentally the same.

Twelve consecutive patients on whom well controlled encephalographic studies with air had been made were subjected to roentgenographic follow-up studies comparable to those made when the anesthetic gases were used. Since the results in this group are also representative of those obtained with the injection of air in general and of the results obtained in this clinic by means of the technic described, they will be discussed in detail. All the encephalographic injections were performed with the patient under anesthesia. Ether was administered to the chil-

dren throughout the period of injection and again during the period of roentgenography to ensure satisfactory results. Tribromethanol in amylene hydrate was used for the adults.

Headaches, moderate to severe in intensity, persisted for an average of one and a half days after the injections, while slight headache, associated particularly with movement or sitting up, lasted for approximately seventy-two hours. Sedatives were required repeatedly by all patients for an average of nearly three days. Nausea usually continued through the first day, and hypodermoclysis was usually necessary. Fluids by mouth and a soft diet were ordinarily tolerated by the second day. The maximum temperature reaction of the 12 patients averaged 38 C. (100.4 F.) at approximately ten hours after the injection.

The roentgenographic studies for these 12 patients were satisfactory. The pictures for 5 showed excellent filling, for 3 good filling and for 4

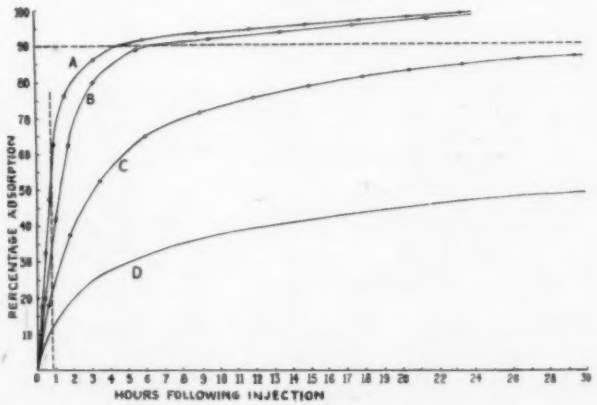

Fig. 2.—Graph showing the estimated absorption rate of gases after encephalographic injection, based on study of serial, follow-up roentgenograms with the following gases: nitrous oxide (*A*), ethylene (*B*), oxygen (*C*) and air (*D*). The ordinate at fifty minutes after injection indicates the average time required for completion of the roentgenographic phase of encephalography; the abscissa at 90 per cent indicates the point of gas absorption at which clinical relief from post-encephalographic reaction is usually obtained.

only fair filling. It should be mentioned, however, as will be brought out later, that in general as many inadequate fillings are obtained with air as with the anesthetic gases presented in this study.

As is indicated in figure 2, the absorption of air was much slower than the absorption of either of the anesthetic gases. The individual variation was great, but the average showed 50 per cent or more of air still present at twenty-four hours and approximately 10 per cent still present at seventy-two hours. Air was found to remain as long as one hundred and forty-four or one hundred and sixty-eight hours in some cases.

COMPARATIVE STUDY

Encephalography with Oxygen.—The use of oxygen in encephalography has been reported on favorably, and the results probably show about as great an improvement over the use of air as can be obtained

TABLE 1.—*Results of Encephalography with Air and Other Gases*

	Air	Oxygen	Nitrous Oxide	Ethylene
Reaction to injection	(Under anesthesia)	(Under anesthesia)	Varied with narcoses; occasionally slight pallor or cyanosis	Varied with narcoses; in children induction of anesthesia alone necessary
Ease of making roentgenograms	Usually easy; continued etherization required in all children	Usually easy; continued etherization required in all children	Usually easy; etherization rarely required	Usually easy; etherization rarely required
Roentgen results				
1. Satisfactory	Usually good	Usually good	Usually good with rapid x-ray technic	Usually good
2. Unsatisfactory filling				
(a) Ventricular	About 16%	.....	.....	About 14%
(b) Subarachnoid	About 11%	.....	.....	About 11%
Headache	Moderate to severe in all adults for average of 36 hours' duration; slight, with movement for average of 72 hr.	Moderate to severe in all adults for 1-2 days; slight with movement for 2-3 days	Usually light; slight with movement for about 24 hr.	Usually light; slight with movement for about 30 hr.
Sedatives	Usually required repeatedly	Usually required repeatedly	Required one or two times only by about one half of adults	None required by half of patients; required more than one to two times by about one third of adults
Nausea and vomiting	Often moderate and prolonged	Often moderate and prolonged	Usually light for 4-5 hr.	Usually light for 5-6 hr.
Fluids tolerated	20 hr.	7-8 hr.	6-7 hr.	7 hr.
Diet tolerated	2d day	2d day	6-8 hrs.	7-8 hrs.
Temperature	38 C. at 10 hr.; normal in 22-30 hr.	38.2 C. at 10 hr.; usually normal in 30 hr.	38.2 C. at 8 hr.; normal in 12-24 hr.	Adults, 37.9 C. at 9 hr.; children, 38.5 C. (rectal) at 9 hr.; normal in 20-24 hr.
Pulse and respiration	Normal	Normal	Normal	Normal
Duration of reaction	Average of 3 days	1-3 days	Usually 12-24 hr.	Average of 30 hr.
Severity of reaction	Usually moderate to severe and prolonged in adults; light to moderate and prolonged in children	Usually moderate to severe and prolonged in adults; light to moderate in children; less prolonged than with air	Usually light in both adults and children, and only occasionally prolonged beyond 24 hr.	Usually light in both adults and children; occasionally prolonged beyond 30 hr.

with ordinary gases. For the sake of comparison, encephalography with oxygen was tried on a few patients with the same technic and the careful follow-up study described in the use of the other gases. The results obtained are in essential agreement with those reported from Penfield's clinic and are presented in table 1. It may be said that in general the

reaction to oxygen, although appreciably less than the usual reaction to air, is considerably more severe and prolonged than that caused by the use of the anesthetic gases, which will be considered next.

Encephalography with Nitrous Oxide.—Encephalography with nitrous oxide was performed 11 consecutive times on 10 patients varying in age from 10 months to 49 years. The clinical reaction to the nitrous oxide was relatively slight and was strikingly less than is usually experienced after encephalography with air. Headache, from slight to moderate in severity and typically occurring in spells, persisted usually for from five to six hours after the injection. Slight headache with movement and sitting up ordinarily persisted for from twenty to twenty-four hours. Aside from 2 patients with an exceptional prolonged reaction, only 1 required a sedative after encephalography with nitrous oxide. It is, however, only fair to say in this connection that of the 7 patients not requiring sedatives, only 2 were adults and that in general children stand the procedure much better than adults.

The patients usually felt somewhat nauseated for four or five hours, and about one half of the group suffered from vomiting of mild degree. Water by mouth was tolerated from six to seven hours after injection, a liquid diet after from six to eight hours and a soft or regular diet after from twenty to twenty-four hours. The temperature usually returned to normal within fifteen or sixteen hours. The pulse and respiration reflected no untoward reaction. Aside from 2 patients with slight pallor and a third with a questionable cyanosis, none of the group showed any immediate reaction to the encephalographic use of nitrous oxide.

Unsatisfactory ventricular filling occurred in 3 instances, 2 of the unsuccessful attempts being made on the same patient. A positive diagnosis was made in 6 of the remaining 8 cases as a result of the encephalograms, the diagnoses agreeing well with the clinical findings. The encephalograms in the other 2 cases, in 1 of which the patient was suspected of having a tumor of the brain while in the other case the patient had a convulsive state of unknown etiology, were normal. Of the 8 cases in which satisfactory filling was obtained, the results were excellent in 3, good in 1 and fair in 4. In all cases the patient remained quiet throughout the period of taking the roentgenograms and the roentgenographic series was obtained without difficulty.

The rate of disappearance of the gas, as observed by comparing the final views with the initial views, was striking, and follow-up roentgenographic studies showed on the average a disappearance of about 90 per cent of the nitrous oxide in five hours. The residual amount disappeared much more slowly, and usually traces could be found up to twenty-four hours. The estimated rate of absorption of nitrous oxide

is shown in figure 2. The slower terminal absorption is perhaps best explained on the basis of impurities of relatively low solubility in the nitrous oxide. Such impurities are known to be present in the commercial nitrous oxide used for anesthetic purposes.

Since, on the average, forty-four minutes was required from the termination of the injection of the gas to the completion of the roentgenographic studies and since from 40 to 50 per cent of the gas had disappeared in this time, the absorption of nitrous oxide was considered to be too rapid to insure the best roentgenographic results. Although the period required for taking the roentgenograms might have been appreciably reduced by performing the injection in the x-ray room and proceeding without delay through the series, from twenty-five to thirty minutes would still have been required, and over this period it was estimated that approximately one third of the gas would have disappeared (fig. 2). Since any retake or special projections necessarily are taken last and these are often the most important from the standpoint of the roentgenographic diagnosis, it seemed advisable to use a gas which would be absorbed more slowly.

Encephalography with Ethylene.[9]—Since the solubility of ethylene is considerably less than that of nitrous oxide,[1b] its trial in encephalography was next undertaken. One hundred successive encephalograms have been made in the University Hospital for patients with the usual conditions requiring encephalography (table 2). Their ages varied from 5 months to 56 years. Sixty-four were adults, and 36 were children (15 years of age or under).

The time required for the injection of the gas averaged ten minutes, extremes of 40 and 275 cc. of ethylene being injected. The average amount for children under 6 years of age was 82 cc.; for children from 6 to 16 it was 100 cc., and for adults (16 years and over) it was 136 cc.

No dangerous reactions were observed. The immediate reaction varied with the degree of narcosis. In 2 patients on whom the procedure of injection was carried out without anesthesia, except for a sedative and procaine hydrochloride locally, the reaction was severe and comparable to that sustained with the injection of air under the same circumstances, e. g., severe frontal headache, vomiting and perspiration. Unlike the reaction caused by air, however, this acute reaction soon passed, and although the patients were aroused by movement, their cooperation was readily elicited, and an excellent series of roentgenograms was obtained in both instances. Of 21 children in whom anesthesia was induced by ether, only 1 reacted to the injection, and

9. The Certified Laboratories Products, Ltd., of San Francisco, contributed the tank of ethylene and valve used in this study.

this child became quiet and relaxed toward the end of the injection. The use of tribromethanol in amylene hydrate (90 mg. per kilogram of body weight being given for adults, and up to 100 mg. for children) produced a more variable narcosis. Supplementary inhalation anesthesia, usually ether, was required in 5 of the 62 adults and in 7 of the 15 children. Of 57 adults in whom tribromethanol in amylene hydrate alone was used, 39 were quiet and 18 reacted to the injection. Eleven of the 18 who reacted to the injection were definitely more quiet and relaxed toward the end of the injection than earlier, an effect in contrast to that ordinarily observed with air. Similarly, of 8 children receiving tribromethanol in amylene hydrate alone, 4 showed a reaction

TABLE 2.—*Analysis of the Roentgenographic Results*

Clinical Diagnosis	Encephalographic Diagnosis: Internal Hydrocephalus	Cortical Scar	Arachnoidal Adhesions	Asymmetry of Subarachnoidal Spaces	Aplasia or Atrophy	Tumor	Porencephalic Cyst	Total Positive	Normal	No Diagnosis: Unsatisfactory Filling	Total Cases
Suspected tumor of the brain	1	..	1	4	3	10	..	13	4	5	22
Convulsive state (idiopathic)	3	..	2	2	5	..	..	9	20	2	31
Convulsive state (traumatic)	1	4	3	1	5	..	5	13	3	2	18
Mental defective	..	..	..	1	1	..	..	1	3	1	5
Cerebral arteriosclerosis	..	..	..	..	..	..	..	..	2	1	3
Encephalitis	..	..	..	..	1	..	..	1	1	..	2
Posttraumatic head syndrome	..	..	..	..	3	..	..	3	1	1	5
Degenerative diseases, central nervous system	..	..	..	1	3	..	..	3	..	1	4
Cerebral aplasia or atrophy	..	..	..	1	4	..	..	4	1	..	5
Psychoneuroses	..	..	..	..	..	..	..	..	2	1	3
Narcolepsy	..	..	..	..	..	..	..	..	1	..	1
Toxic labyrinthitis and polyneuritis	..	..	..	..	..	..	..	..	1	..	1
Totals	5	4	6	16	25	10	5	47	39	14	100

to the injection. All 4 were quieter and more relaxed toward the end of the injection than earlier. Although this delayed narcotic effect of the ethylene is not adequate to overcome the immediate acute reaction of the encephalographic injection, it does materially lessen it.

After encephalography with ethylene, headache of slight to moderate severity was usually observed the same afternoon and evening, with slight headache persisting with sitting up and movement for about thirty hours. As with encephalography with air, there is a wide range of individual variation; in general, the reaction of children is less severe and prolonged than that of adults. Whereas 25 of the 64 adults had moderately severe headache, only 5 of the 36 children had a comparable degree of discomfort. Thirty-seven adults and 26 children had mild headache. The remaining 2 adults and 5 children apparently had little or no headache. Thus approximately 85 per cent of the children and

65 per cent of the adults, or 70 per cent of all patients, had mild headache only. This same impression is borne out by a study of the number of patients who required sedatives after encephalography. Twenty-nine of the children received no treatment, and 7 required an average of 2 doses of sedatives, usually codeine (0.015 Gm.) with acetylsalicylic acid (0.3 Gm.). Sixteen of the adults required no sedatives, and, of the remaining 48, 28 received an average of 2 doses of sedative, while 20 required 5, 6 or more doses, usually codeine (0.03 Gm.) and acetylsalicylic acid (0.3 Gm.).

Nausea ordinarily lasted from five to seven hours. Twenty-three of the 36 children vomited, and of these, 2 of 3 (66 per cent) did so only once or twice—a degree of reaction commonly seen following etherization in children. Only 26 of the 64 adults vomited; over one half of these vomited once and three fourths only once or twice. Fluids by mouth were usually tolerated after seven hours, which made hypodermoclysis unnecessary. A soft or regular diet was usually tolerated the following morning, i. e., approximately twenty-two hours after the injection.

The temperature reaction to the injections reached a peak in an average of nine hours and with few exceptions returned to normal in the course of the following morning. The average temperature reaction in adults was 37.9 C. (100.2 F., orally) and in children 38.5 C. (101.3 F., rectally).

The pulse and respiratory rates were retarded slightly in only 6 patients after the injection of ethylene. Follow-up studies of the cerebrospinal fluid, such as those done in the experimental work previously reported,[1b] were, of course, impossible in this study. In the few instances, however, in which subsequent lumbar puncture afforded an opportunity of studying the cytologic reaction to the injection of ethylene, the results were consistent with those reported in the experimental study and suggested that the cytologic reaction to encephalography with ethylene is not unusual and probably depends more on the amount of gas successfully injected than on the type of gas.

The variation of reactions among the patients with the various clinical conditions in this series is of interest. As a group, the patients suspected of having a tumor of the brain experienced the most difficulty, as might be expected. Although these patients had relatively low grade pressures, as determined by preliminary lumbar punctures in the horizontal position without anesthesia, the reactions tended to be moderately severe and prolonged. Headache persisted for an average of forty-four hours and nausea for fifteen hours. The patients with the syndrome following head trauma also tended to have more severe and prolonged reactions than the average. Those with posttraumatic con-

vulsive disorders usually had slight reactions, but on the average they were prolonged some thirty-four hours. Encephalography was performed on 3 psychoneurotic patients in order to rule out organic lesions. These appeared especially sensitive to the procedure, and their subjective complaints continued considerably longer than the average. The patients with the other conditions as a rule had slight reactions.

In general, 80 per cent had mild reactions, while 20 per cent had moderately severe reactions. Of those patients having a mild reaction, the discomfort was prolonged beyond thirty hours in only 10. On the other hand, 14 of the 20 patients who experienced moderately severe reactions were distressed beyond the average thirty-hour period. Two of the reactions were exceptionally prolonged and simulated a subacute, sterile meningitis. Aside from these 2, only 6 approximated in severity and duration the usual reaction after encephalography with air.

The roentgenographic series was readily obtained for 93 of the 100 patients. The series was obtained with some difficulty and delay in the case of 3 children, and ether was administered to the remaining 4 patients (2 children and 2 adults) to insure satisfactory roentgenographic results. Tribromethanol in amylene hydrate had been given previously to 3 of these patients. The average period required for taking the rontgenograms was forty minutes, and an average of fifty minutes elapsed from the completion of the injection to the completion of the x-ray series. Although this time could be reduced, as already explained, the slower technic was insisted on in this study to settle beyond question the practicability of the gas from the roentgenographic standpoint. Excellent roentgenograms were obtained in 42 cases; 33 of the roentgenograms showed good filling and 11 fair filling, while the results in 14 were unsatisfactory. It should be emphasized that the best roentgenographic results were obtained in the first half-hour after the injection. The poor results were almost invariably due to encephalographic injections which were only partially successful and delayed beyond this period or to a delay beyond forty or fifty minutes in the case of more adequate injections.

An analysis of the roentgenographic results is presented in table 2. The clinical and roentgenographic diagnoses are listed with the number of cases in which the diagnoses were made.

Of 22 patients who were suspected of having tumor of the brain, 13 showed definite roentgenographic findings suggesting pathologic changes and 4 showed pictures considered to be normal. A diagnosis of tumor was made in 10 cases. Satisfactory encephalograms were not obtained in 5 instances. Subsequent operation in 1 of these cases revealed a tumor of the brain, and autopsy in a second revealed an abscess

of the brain. Ventriculograms were made in the other 3 cases. Satisfactory fillings were obtained in 2 of these 3, and in both a diagnosis of tumor was made.

Of 31 patients with a clinical diagnosis of a convulsive state of unknown origin, 9 showed positive roentgenographic findings, 20 normal findings and 2 inadequate filling.

Of 18 patients in whom a convulsive state of posttraumatic origin was diagnosed, 13 showed positive roentgenographic findings and 3 a normal roentgenographic picture, and 2 inadequate filling.

If the instances of inadequate filling are deducted from the foregoing figures, to correspond with the analysis presented in the study of encephalography with air by Stone and Jones,[7] it will be seen that the results are comparable. Stone and Jones reported 14 cases in which filling was unsatisfactory in addition to the 113 cases which formed the basis of their analysis. The ventricles were not demonstrated in 7 of the 113 cases. Thus, of a series of 127 cases in which encephalography with air was done, failure to obtain satisfactory ventricular filling occurred in 21, and failure from the standpoint of visualization of the subarachnoid spaces in 14. In the series of 100 cases in which encephalography was done with ethylene, inadequate ventricular filling occurred in 14, and the subarachnoid filling was unsatisfactory in 11. Demonstration of the subarachnoid spaces in 89 cases showed abnormal results in 38, while in the remaining 51 the results were within normal limits. These results are comparable to those obtained with the use of air as reported by Stone and Jones.

Since the specific gravity of ethylene is almost identical with that of air, and its solubility is such that good roentgenographic results may be obtained when filling is satisfactory, up to one hour, the comparable results obtained with these gases might have been expected. It should be stated, however, that, while the ventricular fillings with ethylene were fully as good as the results obtained with air and the diagnostic demonstration of the subarachnoid spaces was comparable for both gases, the filling of the subarachnoid spaces with ethylene was appreciably less massive than with the use of air. Correspondingly, the large cortical "lakes" of gas, "superfluitant" gas and sagging of the brain observed by Stone and Jones[7] in their follow-up studies on encephalography with air did not occur in this series. Such findings are probably best explained by the prolonged presence of the air. Approximately 79 per cent of air is composed of nitrogen and other even more insoluble gases. The rate of absorption of ethylene, as determined by the estimated rate of disappearance of the gas in repeated follow-up roentgenograms, is shown in figure 2.

It is perhaps worthy of mention that 5 patients have been strikingly relieved of their symptoms after this procedure. Two patients with a syndrome following head trauma and 3 with convulsive states of the idiopathic type have reported relief following encephalography with ethylene.

COMMENT

There is an obvious difference between the duration and severity of the reactions obtained in encephalography with the use of nitrous oxide and ethylene and those in encephalography with the use of air (table 1).

The sedative effect of the anesthetic gases in children insured a satisfactory procedure throughout and necessitated only an initial induction of anesthesia. In adults, when the narcotic effect of the tribromethanol in amylene hydrate was so slight that the initial injection of gas aroused them, the sedative effect of the gas usually resulted in the patient's being more quiet and relaxed through the latter part of the injection and during the period of roentgenography than at the start. This effect was in striking contrast to the usual effect and course of an injection of air under light anesthesia. Thus, in both adults and children the sedative action of the anesthetic gases tended to lessen the severity of the immediate reaction and materially assisted in making the procedure easier and the results more satisfactory.

The rapid absorption of the anesthetic gases, on the other hand, resulted in shortening the reaction after encephalography. Specifically, the period of headache, nausea and malaise was reduced from about three days to one day. Fluids were tolerated the same afternoon or evening, and hypodermoclysis and intravenous therapy usually were not required. A good proportion of the patients did not require sedatives, and the majority of those who did needed them but once or twice. Hospitalization was correspondingly reduced. The economic saving involved is obvious.

The shortened and lessened reaction associated with the use of anesthetic gases in encephalography may justly be considered as a factor of safety in certain instances. A few patients suspected of having a tumor of the brain, with a low degree of increased intracranial pressure, have weathered the reaction to encephalography with ethylene in such a way as could not reasonably have been expected had air been used. Among 14 patients with a diagnosis of tumor of the brain in the series of 100 in which ethylene was used, operation was forced only once. In this connection, it should be added that the accentuation of symptoms and alteration of signs noted by Cairns [10] after injections of air are

10. Cairns, Hugh: Observations on the Localization of Intracranial Tumors, Arch. Surg. **18**:1936-1944 (April) 1929.

usually less marked or are absent after encephalography with the use of ethylene.

As a point of comparative interest, it is perhaps worthy of mention that 4 patients in the series of 100 in whom ethylene was used had previously undergone encephalography with air at other institutions. The enthusiastic testimony of these patients has emphasized, from a subjective standpoint, the difference in reaction, observed clinically after encephalography. One of these patients, indeed, would not believe at first that the procedure had been repeated on him.

Of the two anesthetic gases, ethylene is the more practical. The absorption of nitrous oxide is so rapid that good roentgenographic results cannot be ensured without considerably reducing the period required for taking the films. Undue haste in the roentgenographic technic in many cases undoubtedly would prove to be a distinct disadvantage. This is the limiting factor in the practicability of nitrous oxide.

Three points in the practical aspect of encephalography with ethylene are worthy of emphasis. First, pure ethylene is not explosive, and the danger of the oxygen-ethylene mixture as used for inhalation anesthesia does not exist. The danger of an explosive mixture being formed, with the escape of ethylene into the room on the filling of the bag and initial forcing of air out of the tubing, is negligible, provided large amounts of the gas are not allowed to escape in the presence of lighted matches, cigarets, etc. With ordinary care, the procedure should be entirely safe.

Second, the equipment needed is simple and inexpensive. A small tank of ethylene with a valve may be bought or inexpensively rented from any reliable company handling anesthetic gases. One tank should be adequate for hundreds of injections.

Third, the use of the equipment, according to the method mentioned, is simple and requires little more time than the injection of air. Simple modifications of this technic and the adaptation of other methods to the use of ethylene will readily occur to those interested.

CONCLUSIONS

1. Nitrous oxide and ethylene are safe agents for use in encephalography. Their action is relatively nonirritating and is not associated with bad after-effects.

2. Good roentgenographic results may be obtained with both gases, but the slower disappearance of ethylene makes it more practical for ordinary use. With a good ventricular filling, satisfactory views may be obtained for approximately forty or fifty minutes after the injection.

3. The slight, but definite, sedative effect of ethylene lessens the severity of the immediate reaction to encephalography and materially assists in making the procedure easier and the results more satisfactory. In children the induction of anesthesia alone is required, the sedative effect being sufficient to carry them through the remainder of the procedure.

4. The relatively rapid rate of absorption of ethylene results in a marked shortening of the reaction. The period of headache, nausea and malaise is reduced from about three days, as in the case of air or oxygen, to approximately thirty hours, with a corresponding reduction in hospitalization. Supportive treatment is either not required or is required only to a limited extent.

5. The simplicity of the equipment and technic necessary for the encephalographic injection of ethylene makes the procedure entirely practicable. Within a closed system the pure gas is not explosive and can be used with safety in any of the various methods of encephalography.

CONGENITAL ATRESIA OF THE PELVIC COLON

REPORT OF A CASE

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A case of congenital atresia of the sigmoid colon is reported not only because of the rarity of the condition but because the case illustrates certain points to be observed in the diagnosis of gastro-intestinal conditions in the new-born.

REPORT OF CASE

S., a boy, entered the University Hospital forty-eight hours after a spontaneous delivery with breech presentation after a labor of eight and one-half hours. No meconium was passed during delivery or at any time subsequently, although urine was voided normally. The weight at birth was 6 pounds and 13 ounces (2,996 Gm.). Moderate difficulty was experienced in initiating respiration, and during the first day the legs, hands and face repeatedly became cyanotic. Respirations were shallow and feeble. The infant vomited twice during the first day and then regurgitated frequently during the second day.

Physical examination showed a markedly icteric infant with cyanotic hands and feet. The abdomen was distended, but no masses were palpable. The anus was present, but the canal ended in a blind pouch at a depth of about 6 cm. Laboratory findings included normal urine and 7,700 leukocytes per cubic millimeter of blood.

Roentgen studies showed marked gaseous distention of the stomach and several loops of small bowel (fig. 1*A*). A small amount of barium sulfate was given by stomach tube and was seen in the small intestine in a few hours. The distended loops could not be identified definitely. With the infant in the inverted position and with a thermometer in the anal canal, films showed a canal about 5 cm. in length, seemingly separated from the dilated bowel by a relatively thin partition (fig. 1*B*).

Within a few hours after his admission to the hospital the infant was operated on by Dr. M. H. Manson, ether anesthesia being used. The buttocks and anus were prepared with tincture of merthiolate, and a Kelly cystoscope was introduced into the rectum, which appeared to be normal. It was lined by normal mucous membrane extending from the anal margin for a distance of about 5 cm. At this point visualization was good, and there appeared to be only a blind pouch with a small dark spot at the apex. An alligator forceps was introduced through the cystoscope. Gentle pressure was exerted at the end of the cul-de-sac, but no tear and no escape of gas resulted. Then, with a no. 15 Bard-Parker knife, a tiny nick was made in the end of the cul-de-sac, with a similar result. The hole was explored with the end of an applicator, and the impression formed was that the probe had gone through the pelvic peritoneum. It was not determined whether the large or the small bowel was visualized through the aperture. Because of the

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high position and the uncertainty of what structures were present, it was decided that further manipulation posteriorly was not advisable. There was already a moderate amount of trauma but little bleeding. The infant was returned to the ward and was given saline solution subcutaneously, after which he was returned to the operating room, where the abdomen was prepared with tincture of merthiolate, and the peritoneal cavity was entered on the left side through a McBurney incision, local anesthesia being used. There was a considerable amount of bloody fluid present, which probably came from the manipulation below. A distended loop of bowel presented itself in the wound. This loop resembled colon and was covered by a thin layer of adhesions. No communication between this loop and the large bowel could be demonstrated, and after careful exploration the left lower quadrant, the left lateral gutter and the pelvis were found to be entirely free from any structure resembling bowel. A small urethral catheter was sewed into the

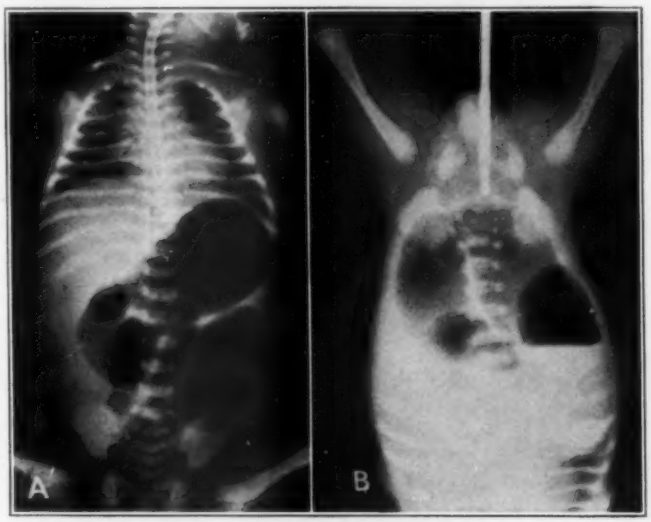

Fig. 1.—*A*, a roentgenogram showing gaseous distention of the stomach and the small bowel. *B*, a roentgenogram taken with the infant in the inverted position and with a thermometer in the anal canal.

dilated bowel, and the abdomen was closed. The infant's condition became progressively worse, and death occurred on the third postoperative day.

The only significant observation at autopsy concerned the intestinal tract. The esophagus and stomach showed no change. The pyloric ring was palpated in its normal position and relation. The entire duodenum was thick walled and extremely dilated, being 3 cm. wide in the collapsed state. There was an angulation at the duodenojejunal junction, but the dilatation and thickening extended about 24 cm. down the jejunum. The enterostomy had been performed at the middle of this jejunal loop. This segment was on the left side of the abdomen, extending down to the position usually occupied by the sigmoid colon. At the pelvis it turned upward again and ended in a mass made up of loops of intestine held firmly together by mesentery and heavy adhesions. The loops were separated by sharp dissection, and three sharp angulations were demonstrated in the mass. The dilatation of the small bowel ended abruptly at this mass, and distally the caliber of

the bowel was normal. It was collapsed through most of its extent but contained small masses of meconium. The cecum lay under the liver and contained meconium. The transverse and the descending colon were normal in position and relation, being small and collapsed. The colon ended abruptly at the brim of the pelvis and distally there was a cord extending to the floor of the pelvis and uniting with the anal canal. The anal canal was normal (fig. 2).

Fig. 2.—Gross specimen showing the marked dilatation of the duodenum and jejunum with the enterostomy tube in place. The angulations in the jejunum and ileum have been freed by dissection. The fibrous cord representing the sigmoid colon is shown connecting the descending colon and the anal canal.

COMMENT

Farr and Brunkow[1] in 1925 stated that the usual incidence of atresia of the intestinal canal is 1 in 20,000 births. Of these, by far the majority are located in the duodenum, about 1 in 10 being found in the colon. Davis and Poynter reviewed all reported cases up to 1922 and found 401 instances of atresia, of which 39 were in the colon.

1. Farr, G. E., and Brunkow, C. W.: Congenital Abnormalities of the Intestine, Arch. Surg. **11**:417-434 (Sept.) 1925.

Congenital atresia is divided into three types by Forssner, according to Andreassi.[1a] First, there may be a complete or an incomplete mucosal membrane interrupting the intestinal lumen. Second, there may be a solid cord connecting the proximal and distal segments. This is made up of serosa, muscularis and submucosa. There may be a complete epithelial lining, scattered epithelial cells or total absence of epithelial elements. Third, there may be two separate segments of intestine, either contiguous or at a distance.

The theories as to causation have been well explained by Cole [2] and by Heckel and Apfelbach.[3] 1. Tandler and Kreuter found the original lumen of the gastro-intestinal tract of most vertebrates to be lost in early embryonic life by epithelial proliferation and later reestablished. They assumed that there was a failure of recanalization. 2. Bland Sutton maintained that atresia occurs at the site of embryonic events, as at the junction of the rectum and anus or at the ampulla of Vater. 3. Vascular disturbances resulting from vascular anomalies, embolism or thrombosis of the mesenteric vessels or intra-uterine twisting of the intestine may be of importance. 4. Defective intestinal rotation has been suggested as an etiologic factor. 5. Chiari mentioned healed intussusception as a cause of atresia. 6. Miscellaneous factors, such as fetal peritonitis, volvulus and syphilis, have also been suggested.

In cases of congenital atresia, the history is most valuable in diagnosis. The important points are vomiting and absence or abnormality of the meconium. Early appearance and severity of vomiting are in direct proportion to the level of atresia. Absence of meconium indicates a relatively low obstruction, and absence of bile pigments places the lesion below the ampulla or else indicates a pathologic process of the bile duct. As Farber [4] and Ladd [4a] indicated, the presence of amniotic fluid in the meconium is of great importance. Atresia occurs before vernix, lanugo and cornified squamous cells develop, and their absence in the meconium therefore is evidence of atresia. Vomiting of amniotic fluid is usually pathognomonic. In imperforation of the anal canal and rectum, Wangensteen and Rice [5] advocated roentgen examination of the

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1a. Andreassi, G.: Considerazioni intorno a un caso di atresia congenita del colon ileo-pelvico, Ricerche di morfol. **11**:375-383, 1931.

2. Cole, W. H.: Congenital Malformations of the Intestinal Tract, Arch. Surg. **23**:820-848 (Nov.) 1931.

3. Heckel, N. J., and Apfelbach, C. W.: Congenital Atresia of the Colon, Am. J. Dis. Child. **34**:1050-1056 (Dec.) 1927.

4. Farber, S.: Congenital Atresia of the Alimentary Tract: Diagnosis by Microscopic Examination of Meconium, J. A. M. A. **100**:1753-1754 (June 3) 1933.

4a. Ladd, W. E.: Congenital Obstruction of the Small Intestine, J. A. M. A. **101**:1453-1458 (Nov. 4) 1933.

5. Wangensteen, O. H., and Rice, C. O.: Imperforate Anus—Method of Determining Surgical Approach, Ann. Surg. **92**:77-81, 1930.

infant in the inverted position, with an opaque disk over the anal plate. Observation of the degree of proximity of the gas bubble in the bowel and the opaque object at the anus will often give valuable data concerning the feasibility of an operative attack (fig. 3). In the case reported here, the three partially obstructed areas in the jejunum in addition to the atresia made a corrective surgical operation too formidable. In reconstructing the details of the case with the roentgen and postmortem observations in mind, it is obvious that the preoperative impression of simple atresia of a small area in the upper portion of the rectum was not well founded. The distention of the stomach and upper reaches

Fig. 3.—Roentgenogram, in the inverted posture, of an infant with imperforation of the anal canal and rectum. The similarity to figure 1*B* is apparent, but in this film the opaque object (shot) rests on the anal plate. In figure 1*B* the thermometer could be introduced into the extrapelvic reaches of the bowel.

of the small intestine, as indicated in figure 1 *A*, indicates clearly that there was an obstruction of the small intestine. As a matter of fact, this was the chief cause of the clinical obstruction, as shown by the segments of distended intestine and as corroborated by necropsy. The small bowel beyond the site at which the mass of adhesions had obstructed the intestine was collapsed, as was the colon. Had the atresia of the pelvic colon been the only obstruction present, the configuration of the distended bowel would have been in the nature of a horse-shoe curve in conformity with the extent of the colon. The distention in such instances is also usually limited to the colon, particularly in obstruc-

tion of the pelvic colon in adults due to carcinoma. As Wangensteen [6] pointed out, vomiting may be absent. The competent ileocecal sphincter limits the distention to the colon by precluding regurgitation of colonic content back into the ileum. In infants with imperforation of the anal canal and rectum, however, unlike adults with acute obstruction of the colon on the left side, vomiting is the rule, despite the fact that the distention usually concerns only the colon.

The contrast apparent between figure 1 *B* and figure 3 sets fairly definitely aside the thought that this lesion might be due to atresia of the upper portion of the rectum. Imperforation of the rectum, as Keith [7] pointed out, concerns essentially the postallantoic intestine. The part of the hindgut which goes to form the rectum is rarely if ever involved in imperforation. In this instance, on the contrary, that portion of the anal canal and rectum which are usually concerned had a lumen, and the atresic area involved the bowel above.

The difficulty of operating on an infant with obstruction of the bowel is a matter of common knowledge. In the case reported here the pathologist had a difficult time unraveling the ensnarled bowel at necropsy. At operation it was believed that the catheter had been inserted into the pelvic colon. The correct operative procedure would have been disentanglement of the obstructed small bowel from the adhesive bands and colostomy proximal to the site of atresia. The newborn infant notably stands enterostomy poorly. In our experience, all infants with congenital atresia of the small intestine on whom enterostomy has been performed have died. About a dozen have survived when an entero-anastomosis was established between the proximal distended segment and the distal collapsed segment (Wangensteen [8]).

It is unlikely in the instance here reported that even if the exact nature of these two obstructions had been precisely identified the infant could have tolerated the corrective procedures necessary to afford adequate relief.

SUMMARY

A case is reported of congenital atresia of the pelvic colon, complicated by an additional obstruction of the small intestine. The criteria which set this unusual form of intestinal atresia aside from imperforation of the rectum are discussed.

6. Wangensteen, O. H.: Vomiting and Distention in Intestinal Obstruction, Journal-Lancet **54**:640-645, 1934.

7. Keith, A.: Malformations of the Hind End of the Body, Brit. M. J. **2**:1736-1741, 1908.

8. Wangensteen, O. H.: Personal communication to the author.

OPERATION ROOM INFECTIONS

CONTROL OF AIR-BORNE PATHOGENIC ORGANISMS, WITH PARTICULAR REFERENCE TO THE USE OF SPECIAL BACTERICIDAL RADIANT ENERGY; PRELIMINARY REPORT

DERYL HART, M.D.
DURHAM, N. C.

During the past five years my co-workers and I have been making a concerted effort to control the occasional sporadic operating room infection occurring in a case of otherwise clean operation. About 90 per cent of the infections have been caused by Staphylococcus aureus, usually of the hemolytic type. Occasionally there has been a mild infection with Staphylococcus albus and rarely a severe infection with Streptococcus haemolyticus.

Beginning with the cleansing of the skin of the patient, the operating room technic was checked throughout. This survey covered the skin of the operative field, the hands of the operating team, the linen used for draping, sponges, autoclaves, sterile water tanks, hot water sterilizers, oil sterilizers, brushes, instruments, gloves, plain and chromic catgut, needles, silk, scalpels and solutions and powder for the hands and gloves. Cultures of these were uniformly found to be sterile. Freshly laundered doctors', nurses' and orderlies' uniforms and blankets and sheets were found to be free from pathogenic bacteria. The shoes worn in the operating room were free from Staph. aureus-haemolyticus, which was responsible for most of the infections.

Cultures of the walls, floors and ceilings of the operating rooms showed an occasional Staph. aureus-haemolyticus. The celotex ceiling in the corridors outside the operating rooms showed large numbers of organisms, both pathogenic and nonpathogenic. Plates of sterile blood agar exposed to the air in all operating rooms for one hour and cultured for from twenty-four to forty-eight hours (fig. 1) showed as high as 78 colonies of Staph. aureus, while the total number of colonies of all organisms at times was as high as 150 (fig. 1*A*).

This work was done in an attempt to solve our local problem and without a complete survey of the literature. Since we became interested in this question the literature has been reviewed, and we are familiar

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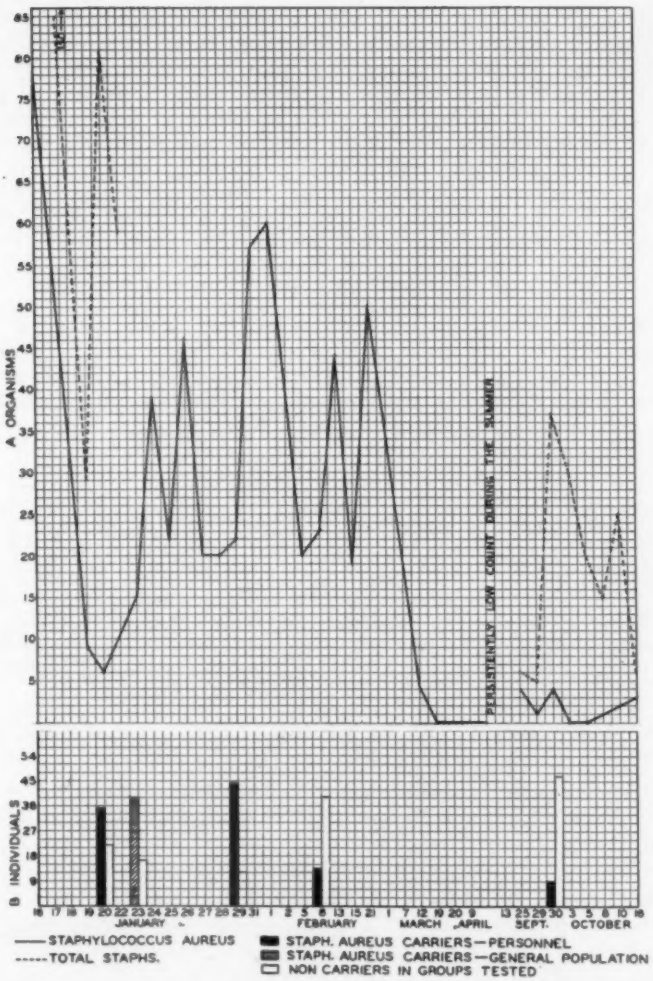

Fig. 1.—*A* shows the contamination of the air in the operating rooms from the beginning of this study and extending through the first nine months. In addition to the seasonal drop for the summer, the number of organisms in the air was reduced (see figure 5 for the highest peak during the following year). Masks 6 by 9 inches (15 by 23 cm.) of six thicknesses of butter gauze 28 by 32 strands to the inch had been worn over the nose and mouth of each member of the operating room personnel during all operations. *B* shows the number of carriers of Staph. aureus (in the nose and throat) among the operating room personnel and in a group taken at random from the general population. There is a definite correlation between the number of carriers and the degree of contamination of the air.

with the work of Meleney,[1] Dandy,[2] Brewer,[3] Goff,[4] Whipple,[5] Davis,[6] Hunt[7] and others. We do not claim originality in much of this work, and refer the reader to the articles cited. We feel strongly, however, that pathogenic organisms in the air contaminated by human beings are responsible for most of our operating room infections. This point, while referred to, has not been sufficiently emphasized; it is placed secondary to contamination of the skin and is not generally considered to be of major importance. The problem of proper masking is referred to in a number of articles, such as those of Davis,[6] Meleney,[1] Walker,[8] Whipple,[5] Doust and Lyon,[9] Kellogg and MacMillan,[10] Blatt and Dale,[11] Leete,[12] Capps,[13] Dannenberg,[14] Mellinger[15] and Weaver.[16] These

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2. Dandy, W. E.: The Importance of More Adequate Sterilization Processes in Hospitals, Bull. Am. Coll. Surgeons **16**:11-12, 1932.

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6. Davis, John Staige: The Importance of Adequate Masking During Operations, Ann. Surg. **100**:1008-1013, 1934.

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9. Doust, B. C., and Lyon, A. B.: Face Mask Infections of the Respiratory Tract, J. A. M. A. **71**:1216-1219 (Oct. 12) 1918.

10. Kellogg, W. H., and MacMillan, G.: An Experimental Study of the Efficiency of Gauze Face Masks, Am. J. Pub. Health **10**:34, 1920.

11. Blatt, Maurice L., and Dale, M. L.: A Bacteriological Study of the Efficiency of Face Masks, Surg., Gynec. & Obst. **57**:363-368, 1933.

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13. Capps, J. A.: Measures for the Prevention and Control of Respiratory Infections in Military Camps, J. A. M. A. **71**:448-451 (Aug. 10) 1918.

14. Dannenberg, A. M.: A Simple Face Mask for Use by Contagious Disease Attendants, J. A. M. A. **70**:990 (April 6) 1918.

15. Mellinger, H. V.: A New Mask That Protects Both Physician and Patient, J. A. M. A. **95**:662-663 (Aug. 30) 1930.

16. Weaver, G. H.: The Value of the Face Mask and Other Measures, J. A. M. A. **70**:76-78 (Jan. 12) 1918; Droplet Infection and Its Prevention by the Face Mask, J. Infect. Dis. **24**:218, 1919.

authors considered the inadequacy of the usual gauze masks, suggested covering the nose and mouth and described new types of masks or a different mesh or thickness. In certain cases there was only a slight reduction in the number of organisms in the air as a result of the suggested change. None of the reports showed that the degree of contamination in the air can be kept as low with human beings present and masked in any way as when they are not present. This, together with the comfort of the wearer, should be the criterion for a satisfactory mask from the point of view of preventing contamination of the air.

The rooms were all repainted, the celotex ceiling was replaced by plaster and walls and floors were washed daily with an antiseptic solution. The incoming air from the forced ventilating system, taken from above

Result of Cultures of the Air Taken in Various Locations in the Hospital *

Date January	Location	Duration of Exposure, Hr.	Staphylococcus	
			Aureus	Albus
19	Accident room	1	0	3
19	Corridor of medical school	1	0	5
19	Autopsy room	1	0	9
19	N. & T. office	1	8	18
19	N. & T. examination room	1	8	7
20	Observation room, students present	1	12	60
20	Sterilizing room	1	1	30
20	Delivery room no. 1	1	0	2
20	Delivery room no. 2	1	0	3
20	Gynec. examining room	1	0	6
21	Instrument room	1	0	0
21	Ventilator duct	1	0	0

* The cultures were made by exposure of blood agar plates in various rooms throughout the hospital and medical school at a time when the bacterial contamination in the operation room was very high (see graph in figure 1 for the air contamination during January). The number of colonies per plate varied with the number of persons and the duration of occupancy. All of the exposures except those made in the examining room and office (N. & T.) used for patients with diseases of the nose and throat, the sterilizing room and the observation room were made when the rooms were unoccupied. These cultures, together with those illustrated in figures 1 to 7, made us feel that the degree of air contamination was dependent on the number of carriers, the degree of infection of their noses and throats and the duration of occupancy.

the roof and washed, was found to be practically free from pathogenic bacteria. Only rarely was a single colony of Staph. albus present on a plate exposed for one hour (fig. 2). It was thought that this might have been brought back from the highly contaminated air in the operating room (fig. 3) to the duct outlet by eddies in the air current.

Cultures of the air taken while the room was unoccupied and with the air agitated with electric fans showed far fewer organisms than were present in cultures taken when the room was occupied and as quiet as possible (fig. 4). It was then found that at times the noses and throats of from 60 to 80 per cent of the operating room personnel contained Staph. aureus, frequently of the hemolytic type (fig. 1 *B*). The same condition was found in a group of persons taken at random from the population outside the hospital (fig. 1 *B*). On any date the number of organisms falling out of the air within a given time varied

Fig. 2.—Petri dish of blood agar exposed for one hour to the clean washed air which was used to ventilate the operating rooms. Most of these cultures showed no growth, but on an occasional plate there were one or two colonies of Staph. albus. These may have reached the plate from the contaminated air of the room (fig. 3).

Fig. 3.—A typical forty-eight hour culture of a sterile Petri dish of blood agar exposed to the air of the operating rooms for one hour during an operation at a time of relatively high bacterial contamination of the air. The colonies were identified as follows: Staph. aureus-haemolyticus, 6; Staph. aureus, 6, and Staph. albus, 32. Even though the usual operations with small incisions can be performed with little risk of infection, we have found that at such a time it is quite dangerous to perform operations of the magnitude of a thoracoplasty or radical amputation of the breast.

directly with the number of persons present and the duration of occupancy (see figure 4 and compare figure 1 with the table). The air of the autopsy room, bacteriologic laboratory, private examining rooms for persons with diseases of the nose and throat and other places throughout the hospital not occupied by a considerable number of persons (table) was less contaminated than the air of the operating rooms. This confirmed our impression that the amount of contamination was determined by the number of persons present and the duration of occupancy. The degree of contamination also varied in the same room under similar conditions at different times of the year, depending on the percentage of persons who were carriers at that time and the intensity of the growth in the noses and throats of the carriers (fig. 1).

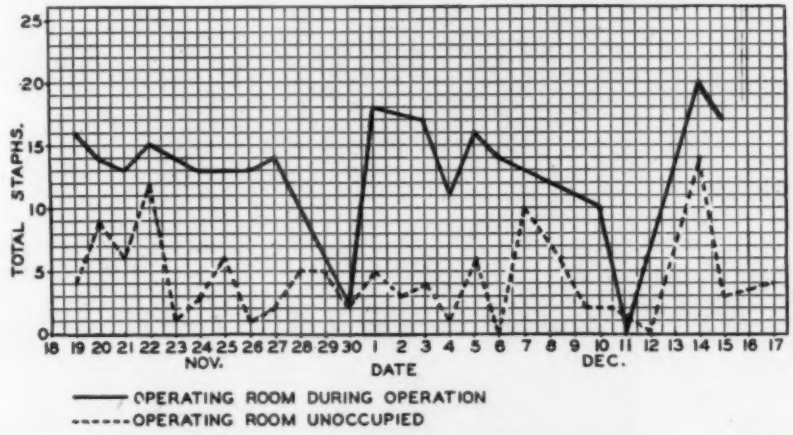


Fig. 4.—Graph showing that the contamination of the air was much less when the room was unoccupied than when it was occupied. A comparison with the table shows also that the rooms occupied only occasionally for only a short time had still fewer organisms in the air. These graphs also show that even though the number of organisms was greatly reduced (compare with figure 1) we were unable to free the air from pathogenic bacteria.

Rigid censorship was placed on a group of three operating rooms. No visitors were allowed; every one entering, including the patients, wore heavy masks over the nose and mouth at all times. No person with an infection of the nose and throat was treated in these rooms, and two masks were worn during all major operations.

An attempt was made to identify all carriers of hemolytic staphylococci, and these persons were not allowed in the operating rooms. It was found, however, that cultures of material from the nose and throat varied from positive to negative from day to day, so that this was impracticable. However, all persons with heavy, persistent infections

of the nose and throat with Staph. aureus-haemolyticus were kept out and treated with bacteriophage and autogenous vaccines until they were free from the organisms. This quarantine and other precautions reduced but did not completely eliminate the contamination of the air with

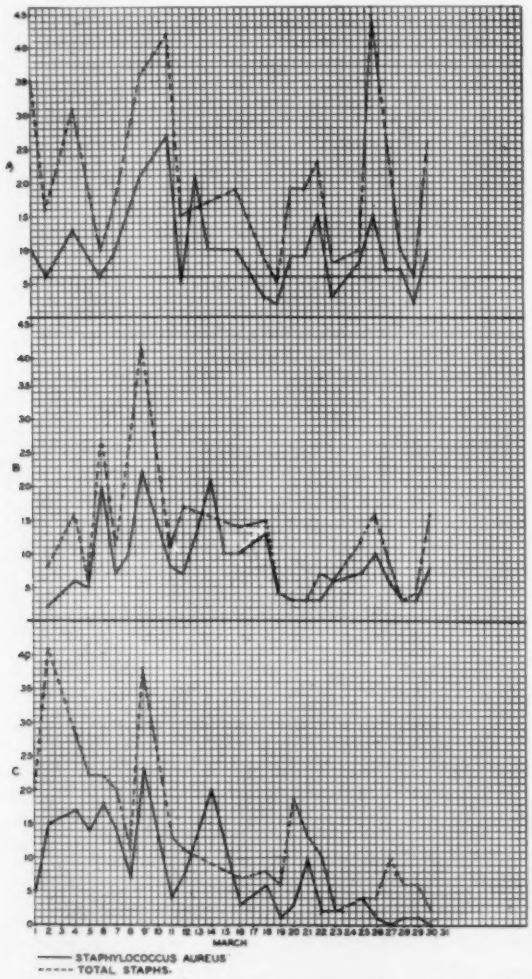


Fig. 5.—In spite of all precautions there were still peaks of aid contamination, at which times the danger of infection in wounds with a large exposed area was great. These peaks were most pronounced during epidemics of infection of the respiratory tract, particularly those occurring during the winter. At such times the same organisms were present in the noses and throats of a large percentage of the operating room personnel (see fig. 1).

hemolytic staphylococci, as shown in figures 5 and 6 (compare figures 5 and 6 with the first part of figure 1). We realize, of course, that other organisms such as streptococci are present at times in the noses

and throats of large numbers of the population and give rise to an epidemic of operating room infections. The surgeon is much more likely to become upset by a streptococcic infection, since the staphylococcic infection is considered to be a contamination from the skin. At most it may incite a change in the preparation of the skin or the scrubbing technic, while the real source of contamination from the air is unsuspected. Any one who doubts the tremendous importance of this contamination from the air need only compare a culture plate exposed to the air for an hour with one inoculated from thoroughly cleaned skin to determine where the greater number of organisms are found.

Double doors were put in so as to prevent currents of air from the wards reaching the operating rooms. The ventilating fans were set

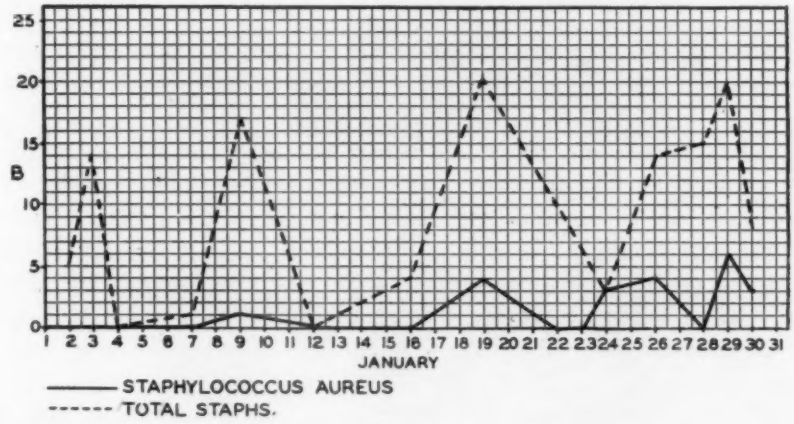


Fig. 6.—Period of low air contamination. At such times there was a relatively low incidence of carriers among the operating room personnel. The contamination in all rooms was correspondingly low.

so that the inflow of clean air (fig. 2) was greater than the outflow, thus forcing a current of air out of all cracks and open doors.

After the institution of these measures there was a marked drop in the degree of contamination of the air (see figures 5 and 6 for periods of high and low contamination and compare with figure 1). There were usually less than 20 colonies in all and less than 5 colonies of Staph. aureus per plate after an hour's exposure during an operation (fig. 6). There were, however, still peaks during epidemics of infections of the respiratory tract when the number of organisms in the air was greater (fig. 5). Many will consider that the large number of staphylococci in the air is peculiar to our location. This is definitely not the case, since every report we have seen in the literature (Meleney from New York, Davis from Baltimore, Hunt from New England, etc.)

gives a higher contamination with these organisms than we have had during the past two or three years.

The total bacterial count seemed to us to be of less significance than the degree of contamination with Staph. aureus, particularly the hemolytic type. Whenever the Staph. aureus count was above 5 colonies per Petri dish exposed for one hour during an operation, we considered that there was danger of an infection occurring in patients on whom an extrapleural thoracoplasty or radical amputation of the breast was performed. In all severe infections which occurred a considerable number of Staph. aureus-haemolyticus had been found on the Petri dish of blood agar exposed during the operation. A graph was plotted showing the daily contamination of the air during operations in all rooms, and all operative procedures necessitating the exposure of a large raw surface were postponed until the contamination was found to be low (compare figure 5 with figure 6). In general, the contamination with the more virulent organisms was greater during the winter months than in the summer and fall. There were, however, periods of low contamination in the winter months (compare January in figure 1 with the following January in figure 6). Patients needing a collapse of the chest were always advised to wait until the summer or fall, when the contamination of the air was persistently low (fig. 1) without the peaks of high contamination so frequently seen during the colder months. Only emergency operations of any type were performed during the peaks of infection of the respiratory tract, at which times we found the contamination of the air to be greatest (compare figure 5 with figure 6).

All major operations requiring exposure of a large raw area, as noted previously, were scheduled only when the contamination of the air was at its lowest and then were posted first in the morning before the room had been occupied long. The ventilating fans were run continuously to replace the contaminated air with clean air (fig. 7). At the end of the operation the wounds were thoroughly washed out with several liters of sterile salt solution. In certain cases the wounds were painted with methyl rosaniline (gentian violet) in the hope that it would inhibit growth of staphylococci. Even with these regulations and precautions, an occasional infection occurred in the patients having more extensive operations (fig. 17). Staph. aureus could be cultured from the incision or drainage tract in 33 per cent of the cases in which extrapleural thoracoplasty was performed. However, only four patients in a series of over one hundred on whom thoracoplasty was done and only one patient of a large number having a radical amputation of the breast died as a result of the infection. Of those remaining, only a few would have been considered infected either from the gross appearance

of the wound or from the clinical course. We do not feel that the incidence of operating room infections in the Duke Hospital was higher than elsewhere in this country. Since the institution of these precautions it is probably lower than is generally encountered where such precautions are not taken.

BACTERICIDAL IRRADIATION

In further attempting to eliminate completely this grave danger to every patient undergoing a major operation, we turned to irradiation with such wavelengths as are known to kill organisms. We first tried a therapeutic ultraviolet ray lamp and proved that we could kill a sprayed culture of Staph. aureus-haemolyticus at a distance of 8 feet

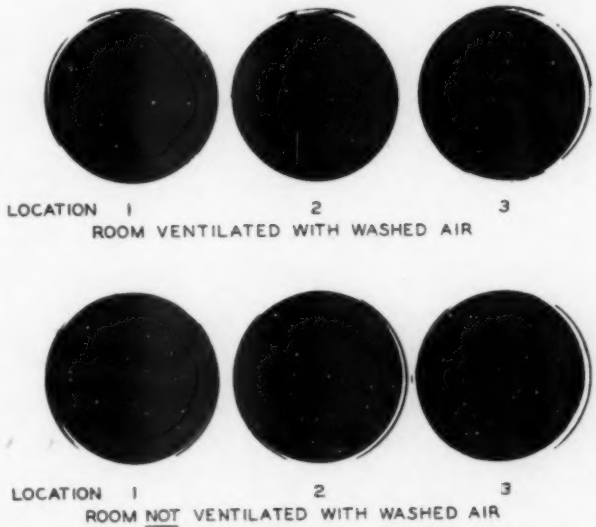


Fig. 7.—Twenty-four hour cultures of sterile Petri dishes of blood agar exposed in the same room under identical conditions and with every precaution taken to keep the room clean except that the lower plates were exposed first without use of the ventilating system while the upper plates were exposed with the ventilating system in use. In both exposures the room was unoccupied except for placing the plates. This "washing out" of the room with clean air did not completely eliminate the pathogenic bacteria. With a number of persons present, recontamination was rapid. With the use of every precaution an occasional infection ocurred.

(243.8 cm.) from the lamp within sixty seconds. The carbon arc lamp was tried but had practically no effect on the organisms.

In the fall of 1934, various manufacturers of ultraviolet ray lamps were asked to cooperate in the experiments to the extent of furnishing the necessary equipment. A favorable contact was made with the Westinghouse Lamp Company, which has conducted extensive researches

in the generation and application of radiant energy, specializing in those regions of the spectrum which were found to be bactericidal. They advised us as to the wavelengths and intensities of radiation which were most efficacious for killing bacteria and least irritating to the tissues and supplied specially designed radiation tubes and other equipment for experimental purposes.

It is well recognized that the germicidal and fungicidal action of radiant energy depends on the wavelength of the radiation reaching

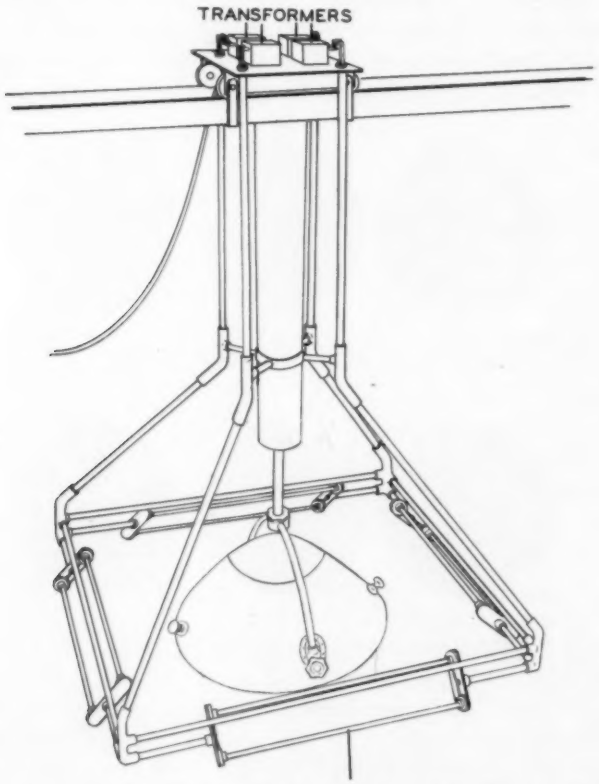


Fig. 8.—Arrangement of the special radiation tubes, each 30 inches long, about the operating room spot light as they were used in the following experiments. This illustration is made from an actual photograph taken from the student's observation room on the upper floor; the outline is inked in and the photograph bleached out. The opposite tubes are 5 feet apart and are so placed that their radiations are directed beneath the spot light. The operative incision and the supply and instrument tables were always exposed to some of the radiations. This arrangement was made with the idea of sterilizing the room if possible but with the definite plan of laying down a barrage of bactericidal radiation of such an intensity that any organisms floating in the air would be killed before they could settle on the supplies and instruments or in the wound.

the organisms. The destructive action of this radiation, such as the erythemal effect when living tissue is exposed, is also dependent on the wavelength and the amount of exposure.

It is at once evident that when long exposures are necessary, as for lengthy operations, it is not only desirable but imperative that the nature of the radiation (wavelength distribution and intensity) used for bactericidal action must be so selected that under all conditions a harmful burning action is avoided.

In designing a source of radiant energy which would prove effective in destroying bacteria, care had to be exercised to see that the intensities of the wavelengths capable of producing detrimental effects, such as erythema, were so low that such effects were practically nil. However, it was also of importance to provide a sufficiently high level of bactericidal radiation to accomplish destruction of the bacteria without the intensity being of such a character as to create any discomfort to the patient. To meet these requirements a special radiant energy device was designed and constructed by the Westinghouse Lamp Company. This device is tubular, has unheated electrodes and utilizes a special mixture of gases in which the discharge takes place with the production of radiant energy of the character mentioned. During operation the tube remains at a temperature only a few degrees above room temperature.

An operating room was equipped with eight of these lamps, each 30 inches (76 cm.) long, as shown in figure 8. Two blood volunteers from among the students were exposed to the radiation from these tubes for eighty minutes and received only a slight reddening of the exposed area, which disappeared within twenty-four hours.

Blood agar plates sprayed with Staph. aureus-haemolyticus and also with a mixture of organisms were exposed to this radiation in the approximate position of the operative wound. The plates were 4 feet (122 cm.) below the center of the cluster of tubes (fig. 8) and 5 feet (152 cm.) from the middle of the individual tubes. With eight tubes operating we could kill a lightly sprayed culture of Staph. aureus-haemolyticus within sixty seconds (fig. 9) or a heavily sprayed culture within less than five minutes (fig. 10). Control experiments showed that radiation did not affect the culture mediums.[17]

It was then determined that in the outlying parts of the room 13 feet (396 cm.) from the center of the cluster of tubes the number of organisms in the air could be greatly reduced within one hour of exposure but not completely eliminated (fig. 11).

17. Many of the cultures were made by Dr. John Devine, who is working with me on the effect of the radiation from these devices on various organisms (to be published).

In the next experiments the tubes were operated for thirty minutes, and then the plates were exposed for one hour after the tubes were turned off. There was a definite reduction in the number of organisms, but the air rapidly became contaminated again.

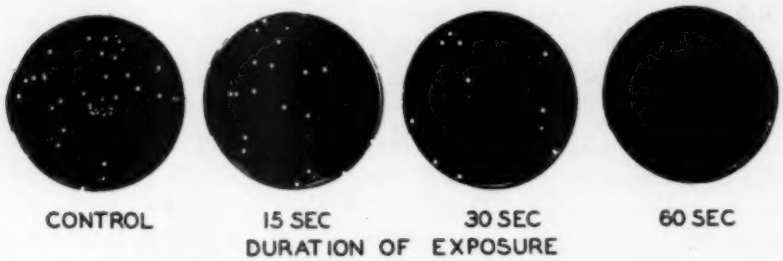


Fig. 9.—Forty-eight hour culture of blood agar plates lightly sprayed with a filtered solution of Staph. aureus-haemolyticus and exposed to the eight tubes in the approximate position of an operative wound (5 feet from the individual tubes). There was a marked reduction in the number of colonies after thirty seconds' exposure and all organisms were killed within sixty seconds.

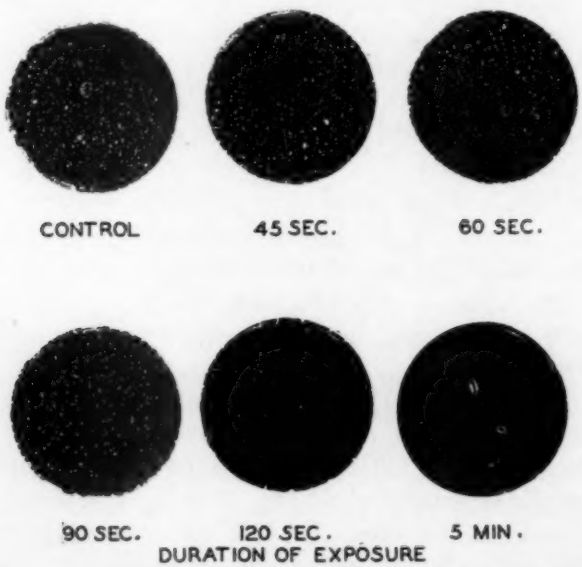


Fig. 10.—Experiment similar to that shown in figure 9, except that the plates were sprayed heavily with an unfiltered suspension of Staph. aureus-haemolyticus. Most of the organisms were killed within two minutes, and all but one colony within less than five minutes. About the periphery of the plates the organisms were shaded from some of the lamps by the edge of the Petri dish and received a less intense exposure and consequently survived for a longer period of time than those in the center. Likewise, where the organisms were in clumps some of them were partially protected and a longer period of exposure was necessary for complete sterilization.

Culture plates of blood agar sprayed with hemolytic staphylococci were then exposed at varying distances from the tubes for periods of time varying from ten minutes to one hour, showing that the time required to kill organisms varied with the distance from the tubes, as in figure 12. Practically all organisms exposed to the radiation from these tubes at a distance of 8 feet or less from the center of the cluster were killed within less than ten minutes and at a distance of 10 feet (304 cm.) within less than thirty minutes. Organisms shaded by the glass edge of the Petri dish were not killed within this time.

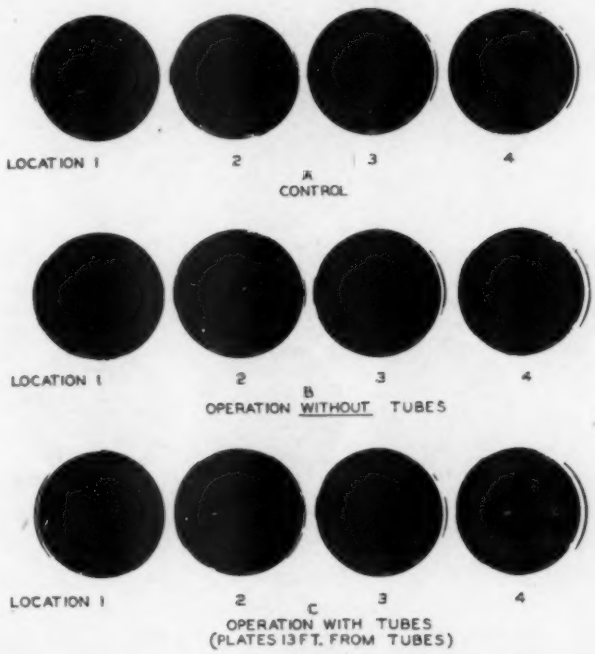


Fig. 11.—Plates exposed in the corners of the operating rooms 13 feet from the center of the cluster of tubes (11 feet from the nearest tube) for one hour and cultured for twenty-four hours. The three exposures were made during three consecutive hours, as follows: while the room was being set up for the operations without the use of the tubes (*A*); during the first operation performed without the tubes burning (*B*), and during the second operation performed with the tubes burning (*C*). Conditions were identical except for the additional personnel necessary for the operations. There was a great reduction in the contamination of the air even at a distance of 13 feet during the operation with the tubes burning, at which time, with more persons and longer occupancy, the contamination of the air should have been at the maximum.

Since there is always a continuous contamination of the air by the operating team and since the outlying parts of the room could not be completely sterilized with the eight tubes in use, it was thought neces-

sary to turn on the tubes during the operations. By this means we hoped to be able to lay down a barrage of radiation which would kill any organism before it could float into the field and drop into the wound. It was felt that if this could be accomplished without injury

Fig. 12.—Petri dishes of blood agar sprayed with a filtered suspension of Staph. aureus-haemolyticus and exposed in the locations shown. The organisms nearest the tubes were quickly killed; those exposed at 8 and 10 feet were killed within less than thirty minutes, while those protected by the shadow of the edge of the Petri dish were not killed within this time.

to the tissues we could eliminate the occasional gross infection. Furthermore, by eliminating contamination of the wound which must always occur but which only rarely goes on to suppuration, we could make

the postoperative course of all patients much smoother. We could also prevent as great a postoperative rise of temperature as occurs in patients operated on without this sterilization of the air. Wounds in rats were exposed for as long as thirty minutes and found to heal as well as, if not better than, those in the control animals for whom the radiation was not used. The peritoneum was exposed for the same length of time, and there was no apparent damage and no resultant adhesions. Wounds in dogs are now being exposed for ninety minutes, and healing is apparently quite satisfactory.[18]

A temporary protection for the staff was devised (fig. 13), and operations on patients were started. Repeated cultures from the air during two successive operations, the first without and the second with the tubes burning, showed that practically all organisms in the air within

Fig. 13.—Photograph illustrating the manner in which the members of the staff were protected. The eyes were covered with goggles of plain glass, which is impermeable to the radiation. An eye shade was also used by some to cover the vents in the goggles. The remainder of the head was covered with a hood of starched cloth. The goggles limit the side vision and tend to become foggy, and it is quite hot beneath the hood. Steps are now under way to provide a more comfortable protection for the operating room personnel.

a radius of 8 feet of the operative incision could be killed (figs. 12 and 14). All exposed supplies and instruments were thus within the effective range of the radiation emanating from these tubes.

From the first trial our results were most gratifying. The patients had less postoperative pain, and healing was more rapid (figs. 15 and 16). All wounds made with the tubes burning maintained throughout the period of healing a dry, scaly appearance (figs. 15 and 16),

18. Experiments on animals have been carried out in conjunction with Dr. Paul Sanger, and these results will be published at a later date.

as contrasted to the occasional moist, slightly macerated appearance of the suture line in thoracoplasties heretofore performed. As contrasted to the high temperature in the occasional patient with an infection of the wound (fig. 17) and the moderate elevation seen in a group of patients with no gross evidence of infection (fig. 18 *A*), there was little rise of temperature in any patients operated on in the field of radiation from these tubes (fig. 18 *B*). Comparable temperature curves

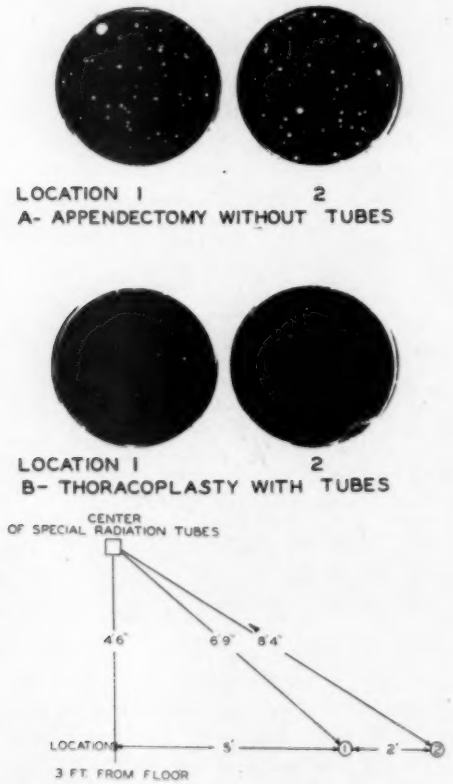


Fig. 14.—Forty-eight hour cultures of sterile blood agar plates exposed to the air for one hour in the locations shown. All conditions, including the operating room personnel, were identical except that the plates shown at *A* were exposed without the tubes burning for the first hour and those at *B* with the tubes burning for the second hour when the contamination of the air should have been greater. Only three colonies are seen in *B*, and one of these is near the rim, where after falling on the plate it was protected from the radiation.

for two days after thoracoplasty in three successive cases in which radiation was used and in three successive cases in which radiation was not used are shown in figure 19. These were taken from the temperature charts used to make the composite curves shown in figure 18 *B*.

Fig. 15.—Photograph of the scar of a thoracoplasty wound nine days after the first stage, at which time parts of four ribs and transverse processes were removed. The maximum elevation of temperature was 38.2 C. (100.7 F.), while the average for the first three days was 37.21 C. (98.9 F.).

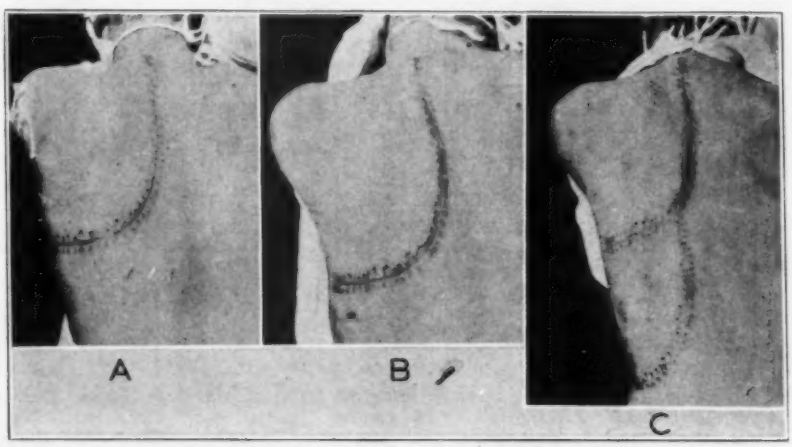


Fig. 16.—Extrapleural thoracoplasty showing the scars of three successive operations for the removal of parts of eleven ribs. This patient was considered to be a poor risk, and delay between stages was longer than usual. *A*, shows the scar eighteen days after removal of part of the three upper ribs. This picture was taken the day before the second stage. *B* shows the scar after the second operation was performed through the scar of the first and parts of four ribs were removed. This picture was taken nine days after operation and one day after the sutures were removed. *C* shows the scar of the third stage the day the sutures were removed and seven days after operation. The upper end of this incision extended into the old scar, so that for a short distance three operative incisions have been made through the same area. The third operation was performed fifteen days after the second. We are afraid to reopen, at such an early date, wounds not produced under this bactericidal radiation because of the danger of infection from organisms which may still be present and in larger numbers than at the time of the original contamination.

They well illustrate the great reduction in the postoperative rise in temperature in all (over fifty) patients so far operated on in the field of radiation from these tubes for various major surgical conditions. The patients were less ill, the convalescence was smoother and recovery was more rapid than had been the case heretofore.

Cultures were made of all drains, but in no case was there a growth. Incisions were reopened (thoracoplasty) within two to three weeks and were closed without drainage (fig. 16); no patient became infected, and there was little elevation of temperature (figs. 18 and 19). The undrained incisions in no case showed enough moisture along the incision or around the sutures to get a satisfactory culture, and no growth could be obtained. This was in sharp contrast to the thoracoplasty

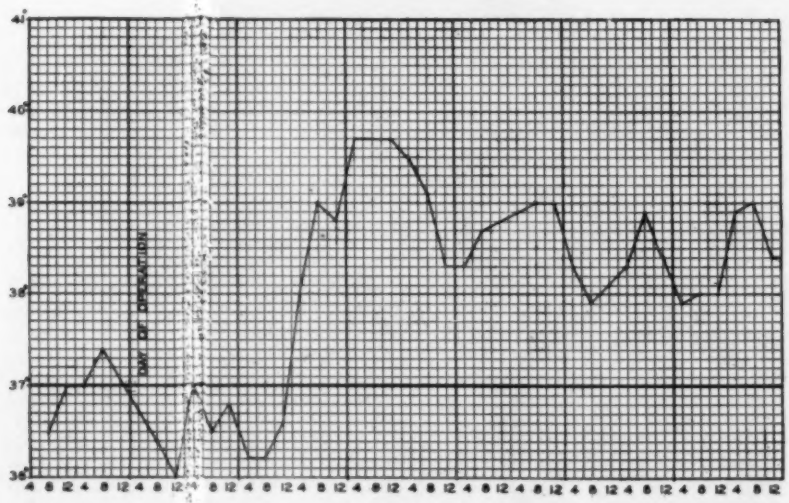


Fig. 17.—Temperature curve of a patient on whom the last thoracoplasty was performed before the introduction of the radiation tubes. The patient, operated on in October, died nine days after operation as a result of an overwhelming infection with Staph. aureus-haemolyticus. Because of the danger of infection, other patients in the hospital for an extrapleural thoracoplasty were discharged to wait until summer or until an operating room could be equipped with special radiation tubes and tests made to determine their safety and efficiency in killing the bacteria in the air.

wounds in earlier cases in which a positive growth of Staph. aureus was obtained from 33 per cent of the operative wounds, most of which were not grossly or clinically infected.

SUMMARY

In attempting to avoid the occasional operating room infection the following facts were established so far as our operating rooms and personnel were concerned:

1. Most of the infections were caused by Staph. aureus-haemolyticus. The organisms entered the wound from the air rather than from the skin of the patient. The air was contaminated by the operating room personnel and patients.

2. While gross infections with suppuration were rare, cultures of drainage tracts and incisions in many cases showed the presence of Staph. aureus-haemolyticus (as high as 33 per cent in cases in which thoracoplasty was performed).

3. All supplies and all procedures in operating room technic were checked by cultures and found to be satisfactory except for the air,

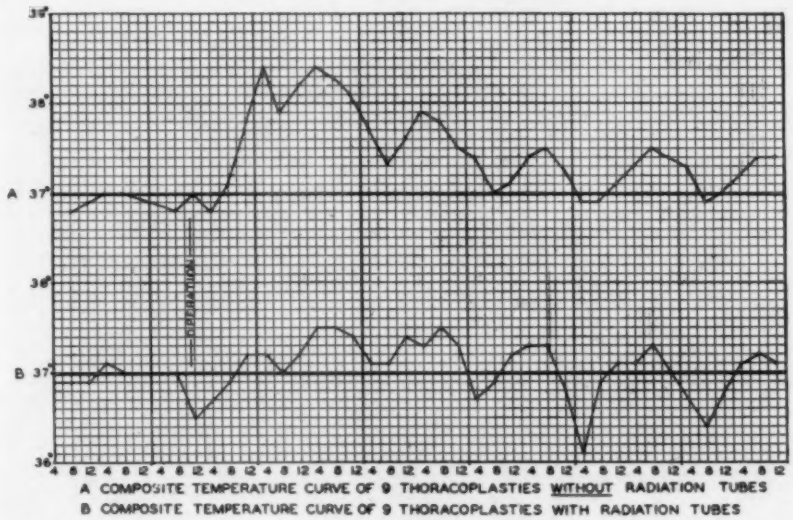

A 37°
B 37°
OPERATION
A COMPOSITE TEMPERATURE CURVE OF 9 THORACOPLASTIES WITHOUT RADIATION TUBES
B COMPOSITE TEMPERATURE CURVE OF 9 THORACOPLASTIES WITH RADIATION TUBES

Fig. 18.—*A* is a composite curve of the temperatures of the last nine patients on whom thoracoplasty was performed during the summer before operation in the fatal case referred to in the legend for figure 17. None of these patients had a gross infection of the wound, and the postoperative clinical course was considered to be normal. Cultures of the wounds, however, showed a growth of Staph. aureus-haemolyticus in 30 per cent of the operations. *B* is a composite curve of the temperatures of the first nine patients on whom thoracoplasty was performed after operation in the fatal case referred to in the legend for figure 17 and with the use of the special radiation tubes. These operations were performed in January and February, during the worst epidemic of influenza and infection of the respiratory tract encountered during the past several years. The temperature curves *A* and *B* might well represent the difference in the entire convalescence of these two groups of patients.

which was heavily contaminated. Staph. aureus-haemolyticus was usually present, at times in large numbers.

4. The operating room personnel and the general population were found at times to have Staph. aureus (frequently hemolytic) in the

nose and throat in as high as 78 per cent of cases, and apparently they were the source of the contamination of the air.

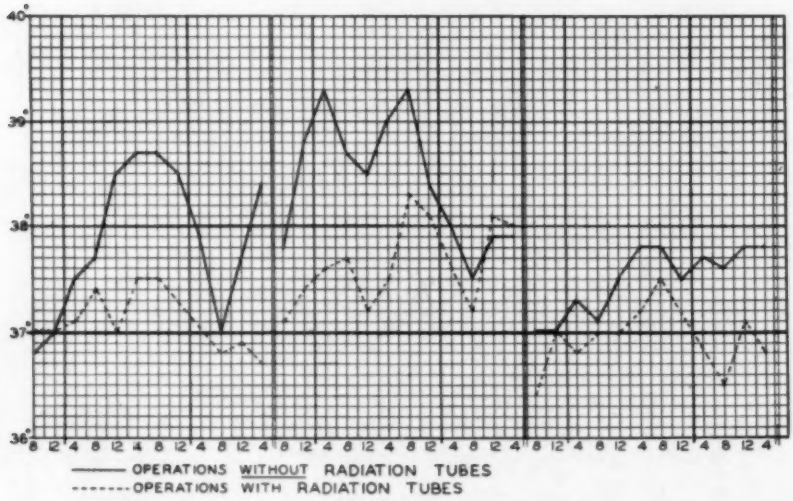
5. During the peaks of air contamination the number of carriers was at the highest.

6. The number of organisms in the air was reduced by from 60 to 80 per cent by the following measures:

(*a*) The number of persons in the operating rooms was cut to the minimum.

(*b*) Masks were worn over the nose and mouth at all times.

(*c*) All persistent carriers of Staph. aureus or of Streptococcus were kept out of the operating rooms at all times.


40°
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8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4
OPERATIONS WITHOUT RADIATION TUBES
OPERATIONS WITH RADIATION TUBES

Fig. 19.—Chart showing the much lower postoperative temperature of the patients on whom thoracoplasty was performed under the radiation. These were taken from the individual temperature charts used to plot the composite curves in figure 18. Each curve, beginning at 8 p. m. the day of operation (approximately the same number of hours after operation), runs for forty-four hours. Only the first three curves for each group are shown, since they are approximately the average for all.

(*d*) The rooms were painted frequently and washed daily with an antiseptic solution.

(*e*) By forced ventilation the contaminated air was replaced by clean, washed air taken from above the roof.

7. The measures noted under 6 did not reduce the number of organisms in the air sufficiently to eliminate all infections. In every case of infection in which cultures of the air had been taken the organism

cultured from the wound was identical with the one cultured from the air during the operation.

8. Tubes specially designed to produce controlled intensities of the most effective bactericidal radiation are now used to sterilize the air with the following results:

(*a*) Sprayed cultures (Staph. aureus-haemolyticus and a mixture of many organisms) were killed at a distance of 5 feet within less than one to five minutes, the time depending on the density of the inoculation.

(*b*) With the tubes burning, practically no organisms could be cultured from the air within a radius of 8 feet from the operative field.

(*c*) In the corners of the room (13 feet from the center of the cluster and 11 feet from the nearest tube) the number of viable organisms falling out of the air was reduced by from 60 to 90 per cent.

(*d*) The air of the entire room could not be completely sterilized within one hour with only eight tubes, as shown in figure 7, and when they were turned off, recontamination quickly occurred if people were present.

(*e*) Blond persons exposed to the eight tubes for eighty minutes at a distance of 5 feet received only slight reddening of the exposed area, which cleared within twenty-four hours.

(*f*) Wounds in rats exposed to the eight tubes at a distance of 5 feet for thirty minutes healed better than in the control animals. No adhesions followed a similar exposure of the peritoneum.

(*g*) All patients operated on under the radiation from these tubes have had an unusually smooth convalescence. There have been no infected wounds, and no culture of material from the wound has shown a growth (approximately fifty patients have been operated on, two for an ulcerated carcinoma of the breast). There have been less elevation of temperature, less pain and a smoother and more rapid convalescence than in the control group of patients.

CONCLUSIONS

It is our opinion that as surgery has embraced operative procedures of greater magnitude and with inevitable trauma, the air-borne organisms have become a distinct hazard. The concentration of operative work by the increased utilization of operating room space has added to the danger of infection from air-borne organisms (in our experience predominantly staphylococci but occasionally streptococci).

It is our opinion, based on experience with this work, that many of the operative wound infections with staphylococci, which heretofore have been ascribed to contamination of the skin, are air borne. These have been combated by meticulously covering the skin, discarding the

knife used for the incision in the skin, changing the methods of preparing the skin, etc., but with little results in reducing the infections. They have recently been eliminated by us in a small series of cases (over fifty) by sterilizing the air with tubes emanating special bactericidal radiation. We do not advocate discarding the precautions used in skin technic, but each surgeon should give critical consideration as to whether the skin or the air is the source of organisms causing these infections. Tubes specially designed to produce controlled intensities of the most effective bactericidal radiation and arranged as shown in figure 8 will kill practically all the organisms in the air within a radius of 8 feet of the operative wound, and it is our opinion that when they are used the so-called skin-contaminated wounds will practically disappear.

The room can be practically sterilized by the use of additional tubes, but at present this does not seem to be necessary. Sterilization of the air should close the last great possible source of contamination of operative wounds. With our small series of patients (approximately fifty) there has been no case in which organisms could be demonstrated in the wound by washings and culture at the operation or at any time during the postoperative course. It is our opinion that it will soon be possible to eliminate almost completely operative wound infections in clean operations.

It should be emphasized that this is a preliminary report on the use of special radiation tubes for the control of air-borne organisms in the operating rooms. Many phases of this work are still under investigation, and it will require a longer time and a much larger series of cases to determine its full value. For us, it has already restored confidence in our ability to establish surroundings in which we can operate without danger of infection from organisms dropping in the wound. We now operate without fear of infection, whereas formerly the dread of bacterial contamination from an uncontrollable source was ever present.

REPAIR OF FACIAL DEFECTS

WITH SPECIAL REFERENCE TO THE SOURCE OF SKIN GRAFTS

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NEW YORK

The repair of a defect on an exposed part of the body, such as the face or neck, presents certain special problems. No matter where a raw surface occurs, it should be covered promptly in order to expedite healing, restore comfort and reestablish proper function. If it is on an exposed area, the added factor of appearance must be considered.

It is not the purpose of this communication to describe the technic involved in obtaining and applying different types of grafts and flaps but to consider their respective suitability for the repair of various defects of the face and neck. The possibilities of deformity in these regions are so vast and varied, owing to a wide range of congenital, traumatic and surgical causes, that to a certain extent each case must be considered an individual problem. Several accepted procedures may suggest themselves for the repair of a given defect, and it is not always easy to decide on the method which best suits the requirements of the particular case.

GENERAL CONSIDERATIONS

So far as it is possible to generalize, the attainable cosmetic result is a decisive factor in the selection of a procedure—subject, of course, to the size, location and etiology of the deformity, the vitality of the surrounding structures, the age and sex of the patient and the simplicity of the methods under consideration. In an old man the cosmetic element would not loom as large as in a young woman, while in the latter appearance is so important as to outweigh even simplicity of technic. The tissues employed in the repair must resemble the surrounding structures as nearly as possible, even if slight additional scarring is entailed, and they must be such as to retain their characteristics in the distant future. The sliding or rotating flap is the ideal procedure in every case, but skin may not be available for this because of the size or location of the defect (figs. 1 to 6).

When a defect cannot be eradicated by approximating the surrounding edges of the skin, the choice lies among various types of free grafts

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and tubed pedicle flaps. Here the determining factors are the accessibility of material, harmony of the transposed skin with its new surroundings and absence of secondary deformity. A graft is not a success merely because it "takes" perfectly; it must match the skin around it in color and texture.

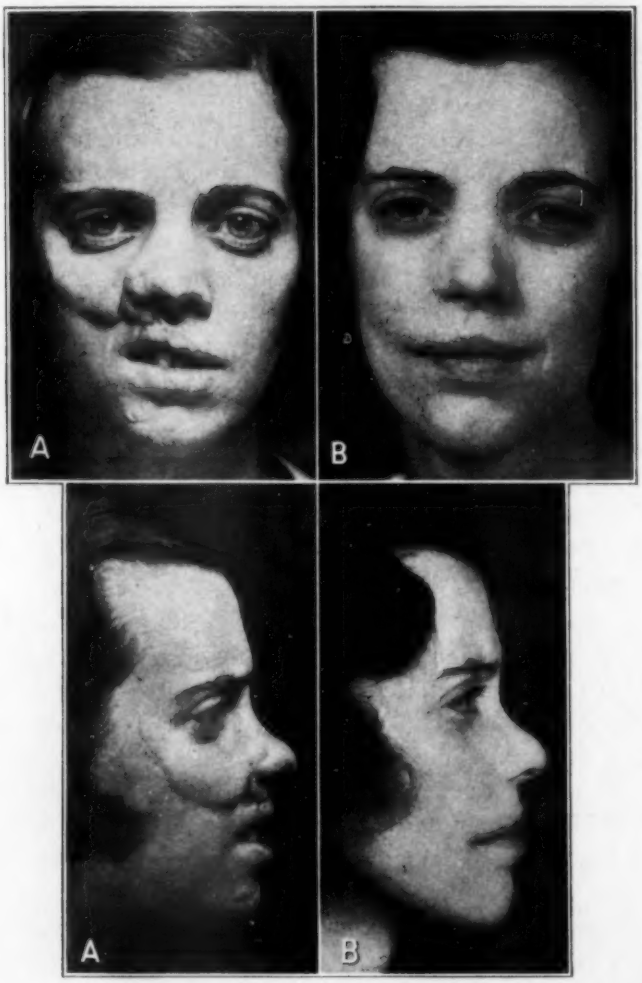

Fig. 1.—*A* shows partial loss of the upper lip, distortion of the lip and nostril, a depressed scar of the cheek and nasal fracture following an injury in an automobile accident. The lumpy area directly under right nostril (fig. 2*N*) is from the displaced skin of the lip which was improperly sutured in the emergency repair. After excision of all scar tissue the curled skin area was flattened out and sutured into surrounding skin, as shown in *B*. The position of the nostril was corrected, and the nasal fracture was reduced. An ascending pedicle flap from the cheek (fig. 2*F*) was sutured into the lip to bring about its normal position.

Since it is extremely difficult to harmonize skin from remote parts of the body with that of the face, a pedicle flap from the forehead, cheek or neck is to be preferred. I advocate these sources in spite of the scarring entailed, as a glaring patch of alien skin is far more conspicuous, in my opinion, than a hair-line scar. Whenever possible, the dimensions of the flap from the forehead are reduced to a minimum by serial excision of the deformity. If the flap is kept small enough, the

Fig. 2.—A drawing illustrating the repair done in figure 1. *F* indicates the ascending flap from the cheek for filling out the defect of the lip; the distorted portions of the lip and nostril were replaced in the position shown by continuous lines (*N*).

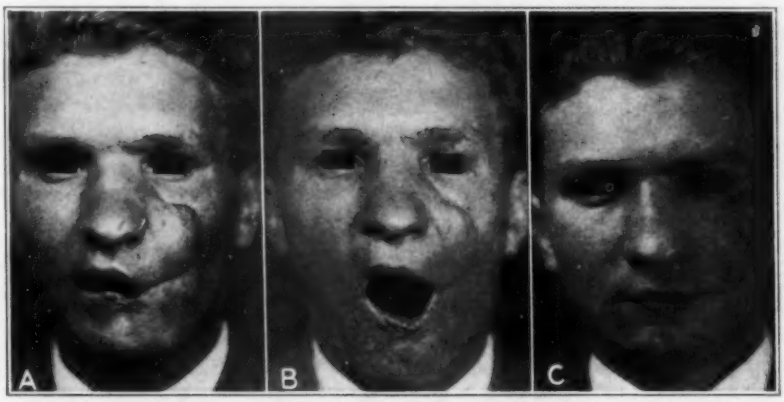

Fig. 3.—*A* shows partial loss of the lower lip with distortion of the mouth following an injury in an automobile accident. The function of the mouth was limited by cicatricial adhesions. The missing mucous membrane and vermilion border of the left side of the lower lip were reconstructed by a mucous membrane flap from the upper portion of the cheek, as shown in *B*. The scarred central portion of the lip involving the mucous membrane and the skin was repaired by shifting of three flaps (fig. 4, *A*, *B* and *C*). *C* shows the final result.

resultant defect can be closed without secondary grafting, owing to the elasticity of the skin of the scalp and forehead (figs. 7 and 8).

From the point of view of color, if for some reason a flap of skin from the forehead is not available, the second choice for use on the

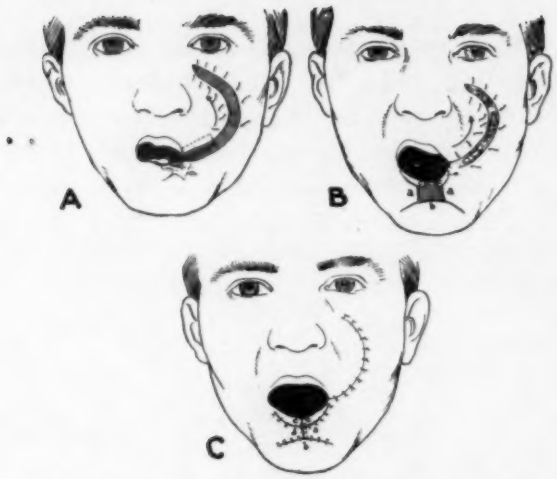

Fig. 4.—A drawing illustrating the technic of repair used to attain the end-result shown in figure 3 *C*. *A* shows excision of the scar of the cheek and the formation of a rectangular mucous membrane flap on the upper cheek (circumscribed in the dotted lines) to reconstruct the left half of the lower lip. *B* shows excision of the central scar of the lower lip and repair of the defect by flaps *a*, *a*, *b*, and *C*, the final result.

Fig. 5.—*A* shows a defect of the cheek in a man of 64 following partial removal of the lower jaw for osteomyelitis. Repair was done by utilizing the surrounding skin for lining and rotating the skin from the cheek and neck to provide the covering with the end-result shown in *B*. By extensive undermining and rotating the facial skin, it is possible to repair large defects which might otherwise require skin from distant parts. The cosmetic end-result is always superior when the methods described here are used.

face is skin from the back of the ear. In most cases the retro-auricular skin is preferable to that of the middle and lower portions of the neck, as the latter presents a marked contrast, even after a period of years, according to my experience. In men, skin from the hair-bearing upper portions of the neck is useful for the reconstruction of hairy facial areas (fig. 8).

Accessibility is a strong argument in favor of the neck as a source of skin for facial reconstruction. A flap from this region can usually be tubed, and the secondary defect is easily closed, with the suture line concealed in the natural folds of the neck. This type of flap is particularly valuable for the replacement of losses in the lower half of the facial skeleton.

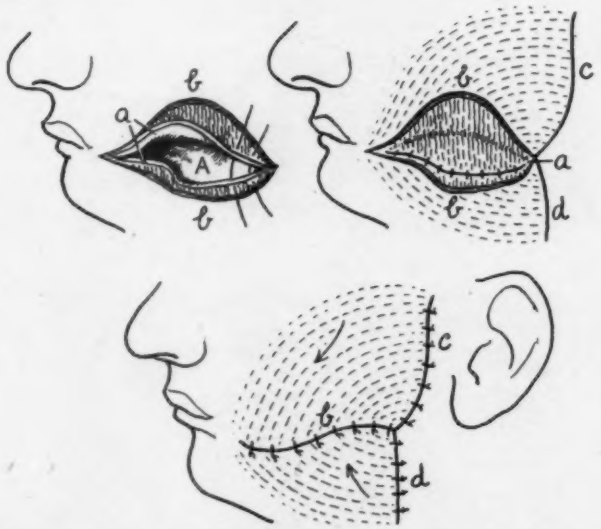

Fig. 6.—Drawing of operative procedure used to attain the end-result shown in figure 5 *B*. The skin turned for the lining is indicated by *a;* the undermined skin of the cheek and neck, by *b,* and the relaxation incisions by *c* and *d*. *A* indicates the tongue.

The ascending flap from the cheek provides a skin supply of excellent quality (figs. 1 and 2), as does the descending flap from the naso-labial fold and the lateral nasal wall; however, the latter type is more subject to limitations of size because of the proximity of the nostril and the inner canthus.

When a large amount of skin has been lost on the face or the tissues surrounding the defect have been devitalized (as by x-rays, radium or malignant disease), skin must be sought on a distant part of the body, but the end-result is hardly ever entirely satisfactory from the cosmetic point of view. The brachial flap, for example, has a good blood

supply, and the transposed skin is very thin, but the color does not match that of the face.

Other common sources of skin flaps for the repair of large facial defects are the abdomen, back and chest (fig. 11).

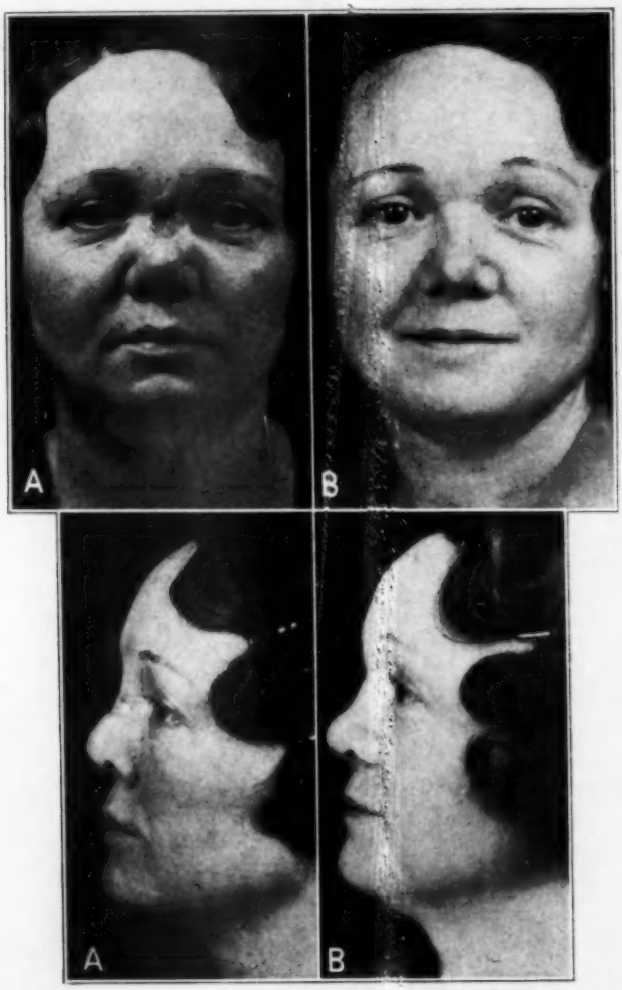

Fig. 7.—*A* shows two views of a woman aged 35 who had paraffin injected into her nose twenty years previously for a saddle-back deformity. Ten years later the nose began to shrink, and the nasal skin was invaded by a paraffinoma. After excision of the involved nasal skin and subcutaneous structures the defect was repaired by a flap from the forehead and insertion of a cartilaginous support from the rib, with the end-result shown in *B*.

In women with hypertrophied pendulous breasts, the posterior mammary surface is another excellent source of skin supply. The skin from

this area is satisfactory for the reconstruction of a large defect, although it is lighter in color than the facial skin; the deformity of the breast can be repaired at the same time.

Comparing the merits of various types of free skin grafts, I favor in general the thin graft (epidermal and dermo-epidermal) for the covering of a large body surface and the full thickness graft on the face, forehead, eyelids and cheeks and on areas requiring pressure, such as the palms of the hands and the elbow. Thus grafts from the upper lids and fine retro-auricular skin are useful for covering defects of the eyelids, wherein the clumsier pedicle flap is too heavy and the

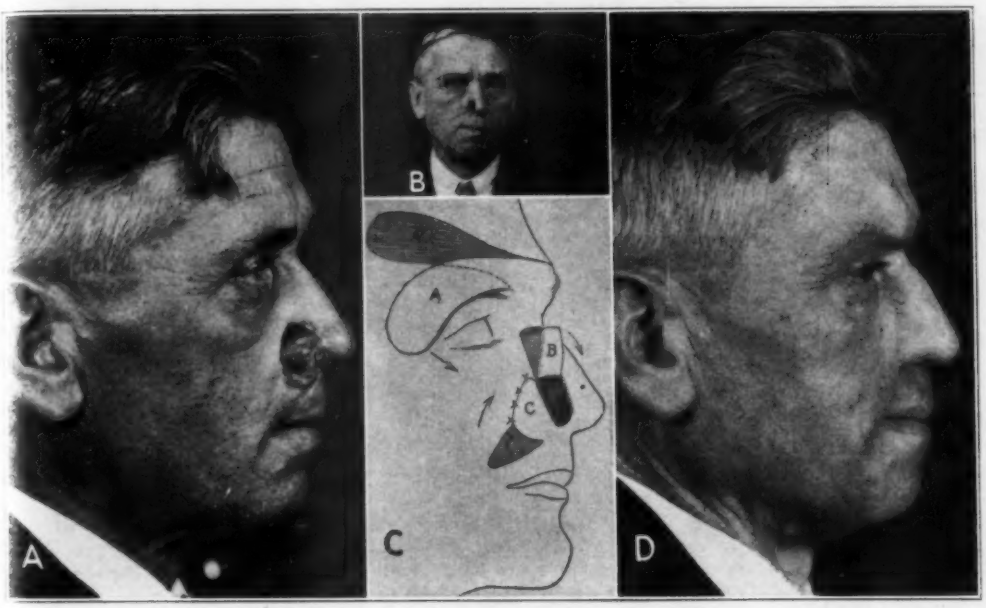

Fig. 8.—*A* shows the loss of the right lower half of the nose, slightly involving the cheek and lip, with a radium ulcer of the floor of the nose and septum. The condition was produced by prolonged radium therapy for epithelioma of the right nostril. Healing of the ulcer was brought about by deep pinch grafting. Reconstruction was started about six months after complete healing of the wound. A small triangular flap was turned up from the nasolabial fold toward the apex of the defect to cover the missing part of the cheek and lip, as shown in *B* and *C*, *c*. *C* illustrates the repair diagrammatically. The skin flap (*B*) is sutured to the freshened edges of the defect, serving as a lining. A flap from the forehead (*A*) was used for covering and a small flap (*C*) from the nasolabial fold to cover the defect in the cheek. The final result after excision of the scar on the forehead is shown in *D*. No skin graft is required to cover this type of defect. Three years after operation was completed there was a recurrence of the malignant growth in the central portion of the upper lip, which required extensive excision of the lip and the central portion of the maxilla.

Thiersch graft is debarred by considerations of color. On the whole, however, the popularity of the split (dermo-epidermal) graft is fully justified by its end-results. Its preparation is more simple than that of the full thickness graft, its "take" is more certain and the cosmetic effect is frequently little inferior to that of the Wolfe graft. I prefer it in numerous circumstances, viz., to cover burned areas on the extremities, to epidermize extensive surfaces of the body, thereby reducing the period of convalescence and avoiding secondary infection and contracture, and to replace mucous membrane in facial cavities.

Often when a defect is replaced, the reconstructed area must be raised because of nondevelopment or destruction of subcutaneous tis-

Fig. 9.—*A* shows the loss of the nostril near the nasal tip, with scarring of the skin and a scar defect of the chin following an injury in an automobile accident in childhood. The patient had an oversized type of nose prior to the accident. The end-result following repair, shown diagrammatically in figure 10, is pictured in *B*.

sues. Full thickness skin, deprived of epidermis, has been used successfully for this purpose.

PARTICULARIZED APPLICATION

The location of the defect is an important factor in the selection of the reparative procedure. For a nasal defect, for example, the skin from the forehead, as I remarked earlier, is so superior to any other in texture and color that it should be used in spite of the added scar. Only if skin from the forehead is not available is a flap from the neck,

chest or arm used. A graft from the eyelid or a retro-auricular graft is indicated for filling out a defect on the nose and upper lip, where shifting of skin is difficult; the color, however, is not as good as that of a flap from the forehead.

Some nasal defects can be repaired by rotating the entire thickness of the nasal wall—skin, cartilage and mucous membrane. This procedure, when done in stages, often obviates the necessity for grafting (figs. 9 and 10).

It is possible to correct a small depression of the middle portion of the nose, especially after submucous resection, by transposing the lateral cartilages, which are fixed at the dorsum.[1] This method of utilizing the surrounding nasal structures has proved satisfactory in my experience.

Fig. 10.—Drawing illustrating the procedures of repair used to attain the end-results in figure 9 *B*. To make possible the correction of the defect in the nostril by shifting the lateral wall, the nose was shortened and the oversized part of the dorsum was removed. The defect (*A*) was covered by rotating the surrounding structures (*a*) and suturing along the line *a'*. The defect in the chin (*B*) was repaired by a tubed flap from the neck *b'*.

Autogenous cartilage is always the substance of choice for repair of the nose and resistant parts of the facial skeleton, such as the forehead, chin and zygoma. In the past few years I have used dermal grafts for filling out facial depressions, and although I have obtained excellent results in all instances, sufficient time has not elapsed to pass final judgment on this medium.

1. Maliniak, Jacques W.: Correction of Nasal Depressions by Transposition of the Lateral Cartilages: A New Method, Arch. Otolaryng. **15**:280-284 (Feb.) 1932.

The split graft, so valuable in nasal reconstruction as a lining, is also useful in replacing missing mucous membrane in the mouth. In postoperative retraction of the lip after operation for a cleft lip, when

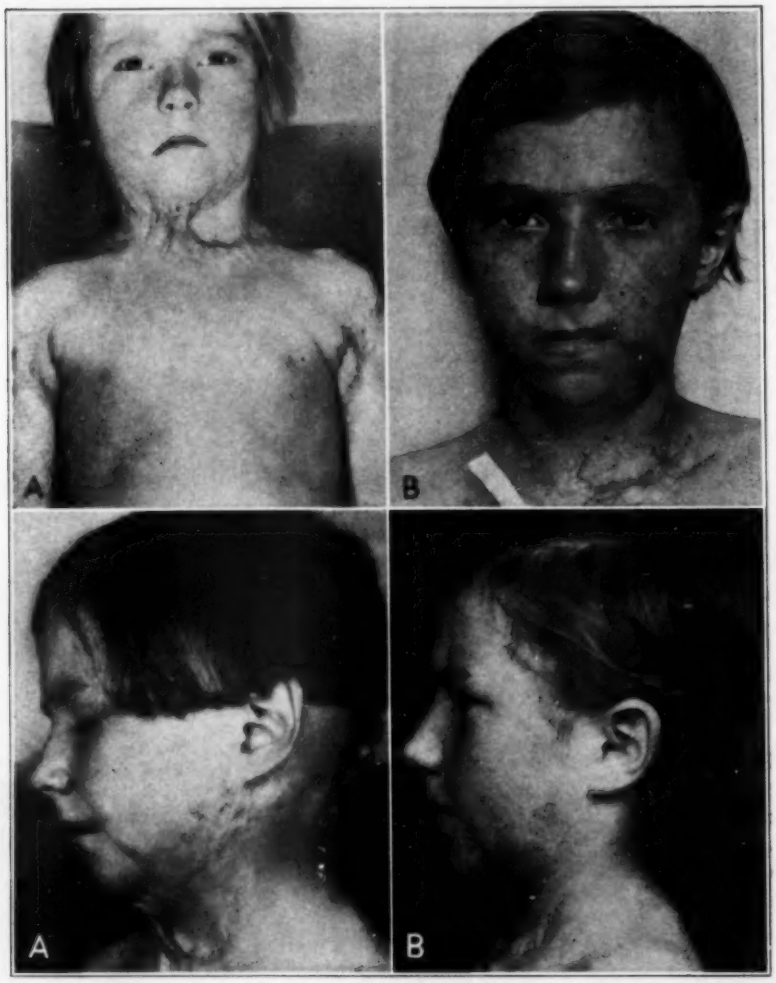

Fig. 11.—*A* shows a burn of the neck and lower part of the face of two years' duration in a girl of 8 years. The thick scar strings extending from the chin to the chest were causing retraction of the chin and downward pulling of the lip. There was loss of the normal contour of the neck. Numerous unsuccessful attempts had been made elsewhere to excise the scars and use a Thiersch graft on the raw surfaces. Complete restoration of the contour of the neck was done by means of a tubed pedicle flap from the lower part of the back and the lateral side of the chest. The color and texture of the skin are of excellent match and can rarely be surpassed by the use of any other procedure. *B* shows the condition a few months after the insertion of the flap.

the sulcus must be deepened for the use of a satisfactory prosthesis, a split graft on a mold may be inserted.

Another important use of this graft is to provide a socket for an artificial eye.

For a defect of the eyelid, a full thickness graft from behind the ear and from the upper lid are used. I consider a graft from the upper lid the first choice, with retro-auricular skin the next resort if skin from the eyelid is not available.

A missing eyebrow is best replaced by a pedicle flap from the opposite brow or by a graft from the scalp.

There are two procedures in general use to cover a large surface on the neck. Some surgeons still employ a split graft. Others prefer a large pedicle flap. The latter, in my opinion, is more suitable because of its cosmetic superiority and the great mobility of the region to be repaired. When it is important to cover a large area on the neck quickly in order to hasten healing and prevent secondary infection and contraction, a thin graft is indicated; but it should be considered an emergency measure rather than the ultimate step in the repair. Often such grafts contract and become wrinkled; almost always their color is poor. Reconstruction is not complete until these cosmetic flaws are eradicated and a harmonious covering is supplied (fig. 11).

The most desirable source of skin for the reconstruction of a defect on the neck, according to our experience, is a pedicle flap from the side of the chest and abdomen. A flap from the upper part of the back is excellent in structure, but the resulting conspicuous scar, high on the back, is distressing to women. For the last few years I have therefore used the lateral aspect of the chest, extending somewhat toward the back and the abdomen. Such a flap is usually tubed and delayed.

The split or full thickness graft is the procedure of choice for the repair of a defect on the hand. A pedicle flap is too thick for the phalanges and small joints of the hand.

SUMMARY AND CONCLUSIONS

Rapid covering of raw surfaces is necessary to expedite healing, restore comfort and reestablish function. On exposed parts of the body the covering supplied must harmonize in color and texture with the surrounding area, even if an additional or more difficult surgical procedure is required.

The sliding or rotating flap is the ideal procedure, but it can be used only for some defects of the face. When sufficient skin is not available, the flap from the forehead becomes the method of choice,

in spite of the added scar. For a defect on the cheek, the combined use of serial excision and a flap from the forehead minimizes secondary scarring and secondary grafting on the forehead. The flap from the forehead is particularly recommended for the restoration of nasal losses.

A tubed pedicle flap from the neck is valuable for reconstruction of the lower half of the facial covering. A large surface on the neck is best covered by a delayed tube pedicle or migrating flap from the lateral aspect of the chest and abdomen.

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EFFECT OF PARTIAL GASTRECTOMY ON GASTRIC ACIDITY

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OMAHA

Partial gastrectomy has in recent years been coming more and more into prominence in the treatment of duodenal ulcer. The all too frequent occurrence of marginal ulcer after gastro-enterostomy has led surgeons to seek some method of approach to the problem of duodenal ulcer by which the acidity of the gastric secretions could be reduced and the incidence of marginal ulcer diminished. The studies of Klein,[1] Lewisohn and Ginzburg,[2] Lewisohn and Feldman,[3] de Takáts,[4] Winkelstein,[5] Crohn,[6] Wilensky and Crohn,[7] McCann[8] and others seem to leave little doubt that after partial gastrectomy there is a definite reduction in gastric acidity.

When one attempts to explain this reduction in acidity, however, one is confronted with a great deal of conflicting evidence; before the value of partial gastrectomy in the treatment of duodenal ulcer can be determined, some more definite information as to its mode of action is desirable. Several years ago Deaver[9] was apparently under the impression that partial gastrectomy removed some of the acid-secreting area of the stomach and that this was the cause of the reduction, but it is now generally admitted that such an explanation is not satisfactory. Friedman[10] and Crohn[6] stated that there is some nerve center located

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3. Lewisohn, R., and Feldman, R.: Ann. Surg. **82**:925, 1925.
4. de Takáts, G.: Am. J. M. Sc. **172**:45, 1926.
5. Winkelstein, A.: Am. J. Surg. **7**:494, 1929.
6. Crohn, B. B.: S. Clin. North America **5**:53, 1925.
7. Wilensky, A. O., and Crohn, B. B.: Am. J. M. Sc. **153**:808, 1917.
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10. Friedman: Zentralbl. f. Chir. **49**:1621, 1922.

near the incisura; that in doing a partial gastrectomy this nerve center is removed and that unless it is removed there will be little reduction in acidity. There has been, however, little evidence shown to substantiate this theory. Babkin,[11] Klein,[12] Ivy and Whitlow[13] and Edkins[14] expressed the belief, and have produced considerable evidence to substantiate their theory, that some reflex or humoral mechanism is responsible. Portis and Portis[15] and Steinberg, Brougher and Vidgoff,[16] on the other hand, stated that the most important factor in reducing acidity after partial gastrectomy is regurgitation of alkaline intestinal secretions into the stomach through the wide stoma produced by Polya's operation. That intestinal regurgitation is a definite entity and the mechanism by which reduced acidity is brought about, we[17] have explained in a previous publication. Walters,[18] in an editorial in a recent issue of *Surgery, Gynecology and Obstetrics,* stated that after partial gastrectomy acidity is reduced "because of dilution and neutralization of the gastric secretions by reflux of intestinal secretions rather than because of actual failure of the remainder of the stomach to secrete hydrochloric acid. Stimulating gastric secretion by injection of histamine in many cases will produce a measurable secretion of hydrochloric acid even after operation has been performed."

Histamine is a stimulus which probably acts directly on the acid-secreting cells of the stomach. It will act on isolated gastric pouches and is in a sense an artificial stimulus. The fact that the acid-secreting cells of the stomach continue to respond to it after partial gastrectomy probably has no important clinical significance as far as proposed operations for duodenal ulcer are concerned. Our investigations were done in an attempt to determine whether there is an actual failure of the stomach to secrete hydrochloric acid after partial gastrectomy, and if not, to evaluate the relative importance of dilution and neutralization in reducing the acidity of the gastric contents.

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11. Babkin, B. P.: Am. J. Digest. Dis. & Nutrition **1**:715, 1934.

12. Klein, E.: Gastric Section: V. Achlorhydria Following Partial Gastrectomy for Ulcer; Studies with Histamine and the Transplanted Gastric Pouch, Arch. Surg. **30**:162 (Jan.) 1935.

13. Ivy, A. C., and Whitlow, J. E.: Am. J. Physiol. **60**:578, 1922.

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15. Portis, B., and Portis, S. A.: Effect of Subtotal Gastrectomy on Gastric Secretion: Experimental Studies by Aid of Pawlow Pouch in Dogs, J. A. M. A. **86**:806 (March 20) 1926.

16. Steinberg, M. E.; Brougher, J. C., and Vidgoff, I. J.: Changes in the Chemistry of the Contents of the Stomach Following Gastric Operations, Arch. Surg. **15**:749 (Nov.) 1927.

17. Hill, F. C.; Henrich, L. C., and Wilhelmj, C.: Surg., Gynec. & Obst. **60**: 966, 1935.

18. Walters, W.: Surg., Gynec. & Obst. **61**:267, 1935.

We[19] have previously shown that after gastroduodenostomy has been performed there is a considerably greater amount of regurgitation of intestinal fluids into the stomach than there is after the two more commonly used operations, gastrojejunostomy and pyloroplasty. The acidity of the gastric contents nevertheless remains high after gastroduodenostomy, in spite of profuse reflux of duodenal fluid. Our first experiments, therefore, enabled us to make a comparison of the effects of gastroduodenostomy and partial gastrectomy with Polya's anastomosis and to determine whether there is sufficiently greater regurgitation after the latter operation to explain the low gastric acidity which it is known to produce.

METHOD AND RESULTS

The test meal used throughout in the present study was a specially prepared[20] 2 per cent concentration of Liebig's meat extract, slightly acidified with hydrochloric acid and containing a small amount of phenolsulfonphthalein. A meal containing meat extract was chosen because it has excellent secretogogic properties and furnishes a normal gastric stimulation. It also remains fluid in the stomach and lent itself admirably to the special chemical studies which we wished to make. Phenolsulfonphthalein was added because when alkalinized it gives the meal a purple color which can be used as an index of the amount of dilution which the meal has undergone in the stomach. Samples of the meal removed from the stomach were compared with a sample of the original meal, and the percentage of dilution, as shown by a lessened concentration of dye, was read directly on a colorimeter.

Experiments were performed on healthy dogs which had been made to fast for twenty-four hours, and the procedure used was the same in all. The amount of the meal given varied between 600 and 900 cc., depending on the size of the dog and the emptying time of the stomach. The amount of the meal was adjusted so that fractional samples could be removed every half-hour for at least one and one-half hours.

A portion of each of the half-hour samples was alkalinized, interfering substances were precipitated with sodium tungstate and sulfuric acid and the concentration of phenol red in each sample was compared on a colorimeter with that of a portion of the original meal similarly treated. The percentage of reduction in the concentration of phenol red in the samples removed from the stomach indicates the number of cubic centimeters of fluid which entered into and diluted each 100 cc. of the original meal during its stay in the stomach. This diluting fluid may be acid secreted by the stomach, a nonacid fluid secreted by the stomach or fluid which has entered the stomach from the small intestine.

We[21] have previously shown that the nonacid fluid secreted by the stomach is small in amount, and for practical purposes it has been ignored in the present investigation. In order to determine the relative amount of dilution produced in the meal by acid secreted by the stomach and by fluid regurgitated from the intestine the

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19. Hill, F. C.; Henrich, L. C., and Wilhelmj, C.: Changes Produced by Various Operations on the Stomach Shown by the Use of the Modified Acid Test Meal, Arch. Surg. **31**:622 (Oct.) 1935.

20. Wilhelmj, C. M.; O'Brien, F. T., and Hill, F. C.: Am. J. Physiol. **115**:5, 1936.

21. Wilhelmj, C. M.; Henrich, L., and Hill, F. C.: Am. J. Physiol. **110**:251, 1934.

following chemical analyses were made by a method previously described:[23] (1) analysis of the acid chloride content of the original meal and (2) analysis of the acid chloride content of each of the samples removed from the stomach. The acid chloride content of each of the samples is compared with the acid chloride content of the original meal corrected for a dilution similar to that of the sample. This correction is made by multiplying the acid chloride content of the meal by the percentage of phenol red in the sample. If the acid chloride content of a sample is greater than the acid chloride content of the meal corrected for dilution, the difference represents the acid secreted by the stomach. If it is less, the difference represents neutralization. We[22] have shown that the concentration of chloride in the secretion of the fundic portion of the stomach is practically all due to acid chloride and averages 578 mg. per hundred cubic centimeters. Thus, by dividing the extra acid choride of a sample (the acid chloride in excess of what the original meal would have at that dilution) by 5.78, the quotient will represent the number of cubic centimeters of acid fluid which was secreted into each 100 cc. of the test meal.

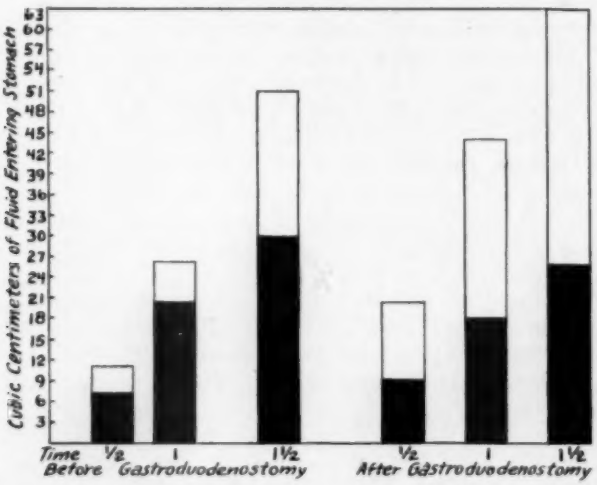

Fig. 1.—Chart showing the cubic centimeters of fluid per hundred cubic centimeters of the test meal entering the stomach of dog A before and after gastroduodenostomy. The columns of total fluid are divided into acid fluid (black) and nonacid fluid (white) and show the findings on fractional samples at half hour intervals.

The reading for phenol red subtracted from 100 gives the total amount of fluid which diluted each 100 cc. of the test meal. The difference between this total fluid and the acid fluid gives the amount of nonacid fluid which diluted each 100 cc. of the test meal.

In figures 1, 2, 3 and 4 we have shown graphically the average results of a large series of experiments done on four dogs before and after operation. Two of the dogs were subjected to gastroduodenostomy, and two, to partial gastrectomy with Polya's anastomosis. When partial gastrectomy was performed, the stomach

22. Wilhelmj, C. M.; Hill, F. C., and Neigus, I.: Am. J. Physiol. **106**: 381, 1933.

was resected at about the level of the incisura angularis, and the portion removed was carefully inspected to be sure that all of the pyloric region, and as little as possible of the fundic portion, were taken. These charts show the total amount of fluid which had entered each 100 cc. of the test meal at the end of each half hour period, and the total fluid is further resolved into acid and nonacid fluid.

In comparing the results of the two types of operation it will be noted that although the total amount of fluid entering the stomach is about the same in both

Fig. 2.—Chart showing the cubic centimeters of fluid per hundred cubic centimeters of test meal entering the stomach of dog B before and after gastroduodenostomy. The findings are indicated as in figure 1.

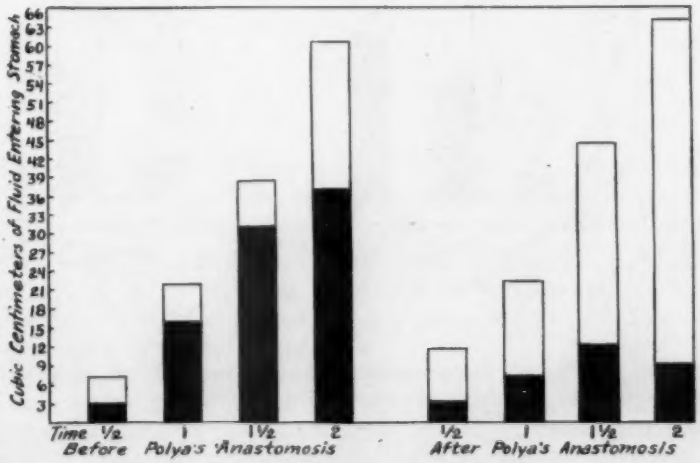

Fig. 3.—Chart showing the cubic centimeters of fluid per hundred cubic centimeters of test meal entering the stomach of dog C before and after partial gastrectomy with Polya's anastomosis. The findings are indicated as in figure 1.

instances, there is a great difference in the amount of acid fluid. In the dogs with resection there is a great reduction of acid, and since there is no correspondingly greater dilution of the meal, the only conclusion possible is that less acid is secreted by the stomach.

In order to obviate the factors of neutralization of secreted acid and dilution of the test meal by regurgitation of intestinal fluids and to demonstrate directly the effect of partial gastrectomy on gastric acidity, another approach was made to the problem by utilizing whole stomach pouches. These pouches, illustrated in figure 5, were of four types. In one type the stomach was separated from the duodenum at the pyloric sphincter, and the ends of the stomach and duodenum were closed. The stomach was then severed close to the esophagus, and the end of the upper stump of the stomach was anastomosed to the side of the jejunum. The opening in the stomach was closed, and a portion of the wall of the closed pouch thus formed was pulled through a stab wound in the abdominal wall to form a gastrostomy opening. Studies were made on this type of pouch for comparison with studies on pouches prepared in a similar manner except that the pyloric end of the stomach

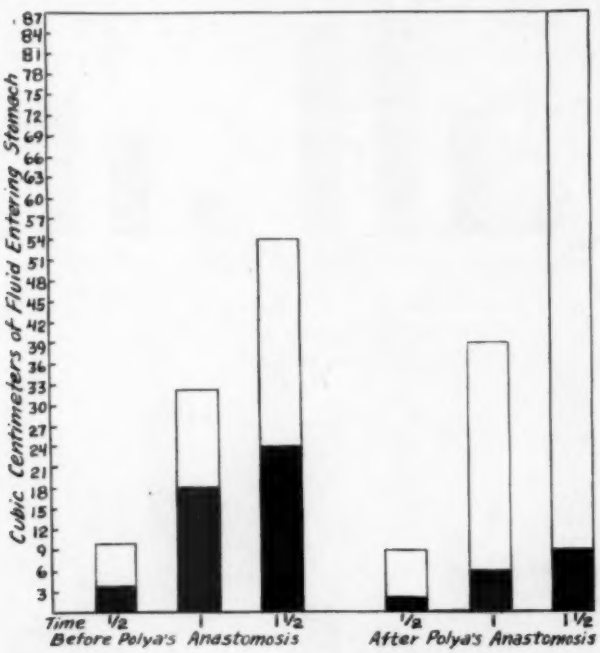

Fig. 4.—Chart showing the cubic centimeters of fluid per hundred cubic centimeters of test meal entering the stomach of dog D before and after partial gastrectomy with Polya's anastomosis. The findings are indicated as in figure 1.

was removed. Both of the foregoing types of pouch are partially denervated, since the stomach has been cut across and many of the nerve fibers coming into it from above have been severed.

The two following kinds of pouch retain their nerve supply, but the continuity of the gastro-intestinal tract is interrupted and fluids were given by hypodermoclysis. Both of these types of pouch were made in two stages, so that the lower stump of the stomach would be healed before the second stage was done, and the studies, which were begun the next day, would not be complicated by hemorrhage from an unhealed suture line. In one type, which was to be used as a control, the stomach was separated from the duodenum at the pylorus, both stumps were closed and gastrojejunostomy was performed with a small stoma. At the second operation, about two weeks later, the opening in the jejunum was closed, and the opening in

the stomach was brought out through a stab wound as a gastrostomy opening. The other type of pouch was prepared in a like manner, except that the pyloric end of the stomach was also resected at the first operation. In one of these dogs a nonleaking fistula of the duodenum was also made, Mann's method being used, and the dog was given food through the fistula.

The meat extract meal was introduced into the pouch through the gastrostomy opening, fractional samples were removed every half-hour for two hours, and acid chloride and phenol red determinations were made on the original meal and each of the samples. The phenol red was used in order to correct for dilution of the meal by mucus secreted by the stomach.

In figure 6 we show the total quantity of acid chloride secreted by the pouches and corrected for dilution. Dog E had a partially denervated pouch with the pylorus intact. Dogs F and G had similar pouches with the pylorus removed. Dogs H, I and J had nondenervated pouches with the pylorus intact, and dogs K, L and M had nondenervated pouches without the pylorus.

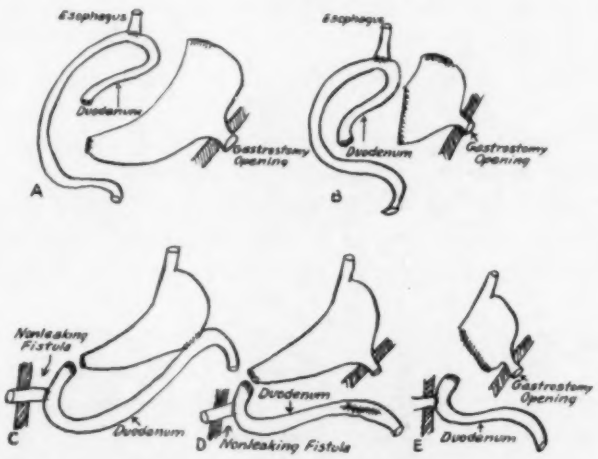

Fig. 5.—Diagrams of the types of whole stomach pouches described in the text. *A* shows a partially denervated pouch with pylorus; *B*, a partially denervated pouch without a pylorus; *C*, a nondenervated pouch with a pylorus, after the first stage of the operation; *D*, a nondenervated pouch with a pylorus, after the second stage of the operation, and *E*, a nondenervated pouch without a pylorus, after the second stage of the operation.

The reduction in the amount of acid secreted in the pouches without a pylorus is so pronounced as to require no comment. We believe that these experiments demonstrate that dilution and neutralization of acid in the stomach by regurgitated intestinal fluids are not a major factor in bringing about the lowered acidity after partial gastrectomy but that the pylorus is a link in the mechanism which causes the fundus to secrete acid. Whether this mechanism is a humoral or a nervous one our experiments do not as yet enable us to say. It will be noted that in none of the experiments has complete anacidity been produced, nor is this to be expected, since we have dealt only with the intragastric

factor. There are stimuli carried to the stomach through the vagus nerves, and there are stimuli arising in the intestine after the ingestion of a meal, both of which cause the secretion of acid by the stomach and neither one of which was affected by partial gastrectomy. Further studies which we have in progress are concerned with these other phases of gastric secretion and will be reported later.

CONCLUSIONS

1. Comparative studies on dogs on which partial gastrectomy and gastroduodenostomy have been performed show about the same total amount of fluid entering the stomach, but after partial gastrectomy the acid constituent of this fluid is diminished.

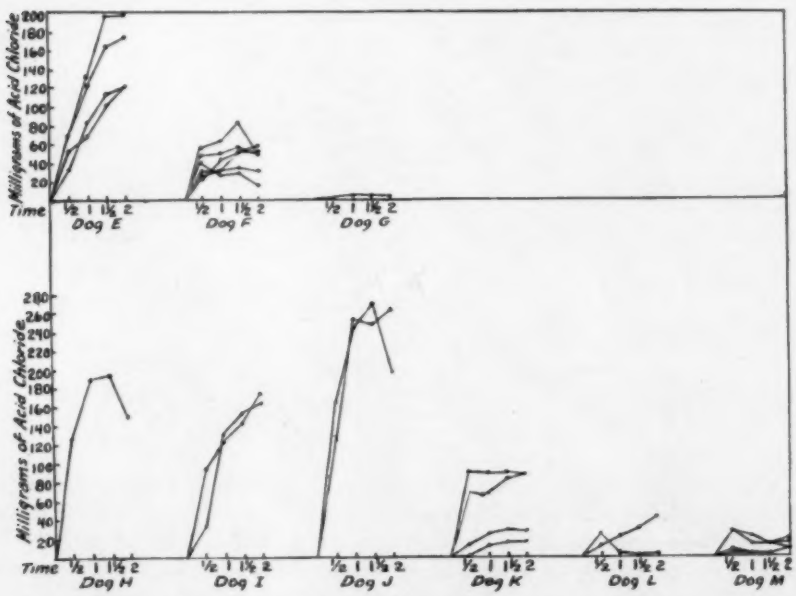

Fig. 6.—Curves showing the total amount of acid secreted by the pouches at intervals of one-half hour, expressed in milligrams of acid chloride. Dog E had a partially denervated pouch with the pylorus intact; dogs F and G had similar pouches with the pylorus removed. Dogs H, I and J had nondenervated pouches with the pylorus intact; dogs K, L and M had similar pouches, but the pylorus had been removed.

2. Studies on whole stomach pouches with and without the pylorus indicate that removal of the pylorus causes a failure of the fundic portion of the stomach to secrete the normal amount of acid.

3. The reduced acidity found after partial gastrectomy is due primarily to the loss of some stimulus arising in the pylorus and not to dilution and neutralization of the acid in the stomach by regurgitated intestinal fluids.

SPONTANEOUS RUPTURE OF THE NORMAL SPLEEN

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AND
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Reported cases of spontaneous rupture of the normal spleen have been appearing in the medical and surgical literature with ever increasing frequency in the past few years. With the exception of Susman's [1] work in 1927, no really critical study has been undertaken to evaluate the cases reported, with the ultimate aim of evolving a rational theory to explain such phenomena. As the subject is one which does not lend itself to experimental study, all work done on it must of necessity be inferential. For this reason, we have made an exhaustive study of the literature, searched out reports of all possible cases, analyzed each case carefully, including one of our own, discarded any which even remotely did not appear to be authentic, and from the remaining genuine cases have developed a concept which, we believe, can explain such phenomena.

That a normal spleen can rupture spontaneously has been the subject of considerable controversy. Ledderhose [2] and Foucault [3] have maintained that spontaneous rupture can occur only in a diseased spleen. Sidney Smith [4] has assumed a similar attitude. However, microscopic examination of the spleen in all reported cases in which sections of the spleen were taken for study has failed to show any demonstrable pathologic process. The conjecture has been advanced by some that the supposedly normal spleen is only apparently healthy, that the spleen is abnormal at one area only, which area is the point of rupture, and that all evidence of pathologic change is destroyed by the disintegration asso-

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From the Department of Pathology, the Beth-El Hospital, Brooklyn, and the office of the chief medical examiner of the city of New York, Dr. Thomas A. Gonzales, acting chief medical examiner.

1. Susman, M. P.: Spontaneous Rupture of the Spleen, Brit. J Surg. **15**:47 (July) 1927.

2. Ledderhose, G., in Billroth, C. A., and Luecke, G. A.: Deutsche Chirurgie, Stuttgart, 1890, pt. 45b, p. 147.

3. Foucault: Les ruptures spontanées de la rate et leur traitement, J. de méd. de Bordeaux **55**:1138, 1925.

4. Smith, S.: Forensic Medicine, ed. 4, London, J. & A. Churchill, Ltd., 1934.

ciated with the rupture. However, it is hard to conceive that an organ as notorious as is the spleen for the widespread dissemination of any pathologic process in it would have all preexisting pathologic process wiped out by rupture. Some microscopic abnormality would undoubtedly be left, either in some unruptured portion of the organ or in close proximity to the point of rupture. Wohl [5] has shown that histologically the spleen ages early. Fifty per cent of spleens from persons 36 years of age show thickening and hyalinization in the malpighian bodies and capsule as well as thickening of the blood vessels. If these early degenerative changes were causative in splenic rupture, one would expect a greater incidence of this condition as well as a greater incidence with increasing age. However, both of these premises are untenable, as spontaneous rupture is a comparative rarity, and in the reported cases the frequency of this condition does not follow the age distribution to be expected if this were so. Another objection raised against spontaneous rupture is the possibility of some remote, perhaps forgotten or unnoticed, trauma. Here again, we have thoroughly scanned the literature and discarded all cases in which even the slightest suggestion of a traumatic history was reported. After such elimination, there still remained cases in which the traumatic element was entirely absent. We are therefore forced back to the conclusion that spontaneous rupture does occur in the normal spleen—normal in both gross and microscopic structure.

REVIEW OF THE LITERATURE

The first reported case, that of Atkinson [6] in 1874, must be regarded as of doubtful authenticity. Although there was no history of trauma and splenic rupture was noted at autopsy, the author's description leaves one in confusion. Just what he implied by "lower portion of spleen disintegrated and in a state of muddy pulp" is highly problematic and forces one to question the normalcy of the spleen before rupture. From the description, it is highly conceivable that the spleen was the seat of a preexisting leukemic or infectious process.

The next reported case, that of Skerritt [7] in 1878, must also be regarded with considerable doubt. Here again, although no history of trauma was elicited and postmortem examination showed splenic rupture, no information as to the gross and microscopic appearance of the organ was given by the author. In the absence of such data it is impossible to pass any opinion as to the normalcy of the spleen before rupture.

5. Wohl, M. G.: Spontaneous Rupture of the Spleen, Ann. Surg. **82**:246 (Aug.) 1925.

6. Atkinson, E.: Death from Idiopathic Rupture of the Spleen, Brit. M. J. **2**:403, 1874.

7. Skerritt, E. M.: Spontaneous Rupture of the Spleen, Brit. M. J. **1**:641, 1878.

Shorten's [8] case must be considered authentic in spite of a history of abdominal injury eighteen months previous to rupture of the spleen. In this instance the finding of a spleen which was both grossly and microscopically normal, as well as the absence of any adhesions to prove a possible previous injury or tear, must negate the importance of the past history of trauma.

The case presented by Connors [9] and the two cases described by Metcalfe and Fletcher [10] were incompletely reported. The authors failed to give any detailed description, either gross or microscopic, which would establish the previous normalcy of the organs they found ruptured.

Capecchi's [11] case must be regarded with some doubt in view of the absence of pathologic studies. The author could not attribute the slight splenomegaly that he found to any cause. However, there is no need to do so, for enlargement per se may be caused by acute congestion, and congestion is part of the picture of spontaneous splenic rupture.

In Stretton's [12] case, although the patient did not give a direct history of trauma, she did give a history of coitus just previous to the rupture. The author suggested the possibility of excessive violence in coitus as an etiologic factor. The element of trauma is thus indirectly introduced into this case.

Again, in Susman's [1] case, despite the absence of a history of direct external injury, one must not lose sight of the fact that the patient bent down to lift a heavy object. It is conceivable that the sudden muscular contraction of the abdominal wall incident to this task might have operated in a fashion similar to external trauma and produced the rupture. At any rate, here again, a spleen both grossly and microscopically normal was found.

In Rhame's [13] case of rupture of the spleen in a young man the history was irrelevant and no significant pathologic changes were observed. The ruptured organs showed some thickening and hyalinization of the capillaries of the malpighian corpuscles and a recent thrombus in the veins at the root of the spleen without any changes in the walls of the blood vessels. The author, however, was skeptical as to the

8. Shorten, W. W.: Apparent Spontaneous Rupture of a Normal Spleen, Brit. M. J. **2**:844 (Dec. 27) 1919.

9. Connors, J. F.: Ruptured Spleens, Ann. Surg. **74**:1 (July) 1921.

10. Metcalfe, R. F., and Fletcher, L. Z.: Ruptured Spleen, Ann. Surg. **75**:186 (Feb.) 1922.

11. Capecchi, E.: Spontaneous Rupture of the Spleen, Policlinico (sez. prat.) **32**:665 (May 11) 1925.

12. Stretton, J. L.: Abdominal Cases Illustrating Important Surgical Principles, Brit. M. J. **1**:901 (May 29) 1926.

13. Rhame, J. S.: Spontaneous Rupture of the Spleen with Venous Thrombosis, Ann. Surg. **88**:212 (Aug.) 1928.

occurrence of spontaneous rupture and advanced the view that the existing pathologic process might have been wiped out at the time and site of rupture. This view has already been discussed.

The case reported by Underwood [14] presents several elements of doubt. Although the spleen was found to be microscopically normal, there were old adhesions posteriorly and at the right upper pole, as well as a slight degree of fibrosis and hyaline degeneration of the blood vessels, together with some pigmentation. These factors, especially the old adhesions and the pigmentation, suggest some previous pathologic process, although what are loosely and commonly called adhesions are often aberrant peritoneal reflections, having none of the pathologic significance implied by the term "adhesion." [15]

Harvey's [16] case, in which the spleen was slightly larger than normal and microscopy showed no abnormalities, is unquestionably authentic. Here also, the author noted a few adhesions at the upper pole, which, as explained before, might well have been some aberrant peritoneal reflections.

Bailey's [17] case meets all the requirements for the spontaneous rupture of a normal spleen in regard to both the history and the histologic picture. Yet the author, in spite of a carefully taken history, expressed the belief that there may have been an element of trauma that was either forgotten or overlooked by the patient.

In Byford's [18] presentation, microscopy of the spleen showed an increase in fibrous elements, with marked thickening and hyalinization of some of the blood vessels. As has been pointed out before, Wohl has shown that this is a normal occurrence in a large proportion of spleens and is not to be taken as evidence of a previous pathologic process. Byford's case must therefore be considered genuine.

Nixon,[19] in reporting his case, mentioned only slight enlargement of the spleen but failed to give any gross or microscopic description of the organ. This is due to the fact that at operation mattress suturing of the spleen and not splenectomy was done and that after the death of the patient autopsy was not performed. There was no history of trauma.

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14. Underwood, W. E.: Spontaneous Rupture of the Spleen, Brit. M. J. **1**:1118 (June 22) 1929.

15. Stockard, C. R.: The Trend of Morphology, Science **69**:363 (April 5) 1929.

16. Harvey, T. W., Jr.: Spontaneous Rupture of the Spleen, J. A. M. A. **93**: 987 (Sept. 28) 1929.

17. Bailey, H.: Spontaneous Rupture of the Normal Spleen, Brit. J. Surg. **17**: 417 (Jan.) 1930.

18. Byford, W. H.: Spontaneous Rupture of the Normal Spleen, Arch. Surg. **20**:232 (Feb.) 1930.

19. Nixon, P. I.: Spontaneous Rupture of the Normal Spleen, J. A. M. A. **96**:1767 (May 23) 1931.

Demel's [20] case must be excluded because it introduces the questionable factor of a retrograde thrombosis secondary to an embolic process. It is, furthermore, too vaguely described from the point of view of this paper.

In Black's [21] case the spleen again showed some thickening and hyalinization of the central arteries. This finding, as shown before, is to be disregarded and the case accepted as genuine.

In Dardinski's [22] case, in addition to spontaneous rupture of a normal spleen, there was an irregularly enlarged nodular liver (primary malignant hepatoma of the liver). The author expressed the belief that the rupture was due to an increase of pressure in the organ as a result of a damming back of blood from the liver. That the local congestion played a part in the rupture is possible, but it must be remembered that such congestion, caused by obstruction to the splenic venous circulation either within the liver or in the portal vein (Nobel and Wagner [23]) or found even in association with severe cardiac failure, is a common occurrence in spleens that do not rupture. This suggests that other factors not discussed by the author were operative in this case.

Kaspar [24] reported an interesting case in a young man and suggested that an unusual digestive hyperemia of the spleen might have had something to do with the rupture.

Halliwell [25] presented an interesting case in which the splenic pedicle was unusually long. He took exception to the view that there might have been a forgotten injury in his patient and pointed out that although the spleen has better protection than the intestines or the kidneys against possible trauma, yet it alone ruptures spontaneously.

Bohler's [26] case presents the same difficulty as does Susman's.[1] Here also there was a history of the patient's bending to lift a heavy object, with the possibility of the sudden muscular contraction and increased intra-abdominal pressure acting as a traumatic element.

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20. Demel, V. C.: Di un caso di rottura spontanea della milza, Riforma med. **47**:522, 1931.

21. Black, J. M.: Spontaneous Rupture of the Spleen, Brit. J. Surg. **20**:526-(Jan.) 1933.

22. Dardinski, V. J.: Spontaneous Rupture of an Apparently Normal Spleen, J. A. M. A. **99**:831 (Sept. 3) 1932.

23. Nobel, E., and Wagner, R.: Die Thrombose und Phlebitis der Milzvene im Kindesalter („Milzvenenstenose"), Ergebn. d. inn. Med. u. Kinderh. **45**:1, 1933.

24. Kaspar, M.: Ein Fall von Spontanruptur der gesunden Milz, Beitr. z. klin. Chir. **156**:97, 1932.

25. Halliwell, A. C.: Spontaneous Rupture of Normal Spleen, Brit. M. J. **1**:919 (May 27) 1933.

26. Bohler, E.: Eclatement du hile de la rate au 7e mois de la grossesse, Bull. Soc. d'obst. et de gynéc. **22**:707 (Oct.) 1933.

Abell [27] neglected to give the results of the microscopic examination in the case that he reported.

The splenomegaly in the case reported by Smith, Morrison and Sladden [28] was found to be due to an intense congestion of the sinuses and not to any intrinsic pathologic process in the spleen.

Lundell [29] and Dahle [30] each reported an unquestionably genuine case, as did Basso,[31] in a patient in whom autopsy revealed an unsuspected spontaneous rupture of a normal spleen.

In Burnett and McMenemey's [32] case the slight splenomegaly found was shown by microscopy to be due solely to congestion.

In the last reported case, that of Young,[33] there were no doubtful features, and examination of the spleen suggested that some violent internal force, such as increasing engorgement of blood, may have been at work to cause explosive tears in the capsule.

REPORT OF A CASE

The case we are presenting is interesting for two reasons: In the first place, it is a genuine case of spontaneous rupture of a normal spleen, and in the second place, it casts some light on what we believe to be the mechanism of spontaneous rupture.

History.—A white woman aged 29, thirty-two hours prior to her admission to the hospital, had a sudden nonradiating pain in the left upper quadrant of the abdomen and in the left flank. The pain was not associated with chills, urination or hematuria. It remained localized to the left upper quadrant and left flank for the next twenty-four hours, but with lessened intensity. Just previous to her admission to the hospital the patient complained of some epigastric distress and vomited twice. She was seen by an ambulance surgeon at home but was not hospitalized until four hours later, when she was found in shock. Subsequent questioning of the physician who saw the patient before the ambulance surgeon, as well as of the latter, failed to disclose even the slightest suggestion of a history of trauma. Both had inquired closely on this specific point; both stated, further,

27. Abell, I.: Wandering Spleen with Torsion of the Pedicle, Ann. Surg. **98**: 722 (Oct.) 1933.

28. Smith, A. H. D.; Morrison, W. J., and Sladden, A. F.: Spontaneous Rupture of the Spleen in a Pregnant Woman, Lancet **1**:694 (April 1) 1933.

29. Lundell, G.: Ueber spontane Milzruptur, Acta chir. Scandinav. **75**:547, 1934.

30. Dahle, M.: Ruptur von normales Milz ohne bekannte Ursache-Spontanruptur? Acta chir. Scandinav. **75**:519, 1934.

31. Basso, R.: Rottura spontanea della milza nel decorso di un'angina, Gior. veneto di sc. med. **8**:275 (March) 1934.

32. Burnett, E. C., and McMenemey, W. H.: Rupture of the Normal Spleen in Pregnancy, Brit. M. J. **1**:1122 (June 1) 1935.

33. Young, R. D.: Spontaneous Rupture of a Normal Spleen, Ann. Surg. **101**:1389, 1935.

that there was not the slightest suggestion even of unusual physical activity at or before the onset of symptoms for at least three or four days before the patient was seen.

Physical Examination.—The patient was markedly anemic, with extreme pallor of the lips and finger-tips. All mucous membranes showed extreme pallor. She was semicomatose, with a respiratory rate of 30 and a pulse rate of 140, the beat being thready in character. The head and neck showed no abnormalities. The lungs were clear. The heart sounds were regular, with a rate of 140, and were of poor quality and without any bruits. The abdomen was distended over the lower portion, particularly the right side. There was tenderness in the epigastrium in both upper quadrants and in the left lumbar region. A positive Murphy sign was found on the left side. The spleen was palpable 2 fingerbreadths below the costal margin. The edge of the liver was not felt. There was no area of dulness in the flanks. The extremities were normal. The temperature was 99 F. Examination of the blood showed a count of 17,000 white cells, of which 80 per cent were polymorphonuclears and 20 per cent were lymphocytes. The hemoglobin content was 58 per cent (Sahli).

Tentative diagnoses of pancreatitis and ectopic gestation were made, the latter in spite of the fact that the patient's last menstrual period occurred ten days before admission to the hospital. The surgical staff was called in consultation, and internal hemorrhage was considered the cause of the shock. Before antishock measures could be instituted, the patient died.

Autopsy.—Examination was performed one-half hour after death. The peritoneal cavity was filled with much blood and clots, chiefly in the pelvis and the left gutter. The spleen measured 17 by 9.5 by 5 cm. and weighed 385 Gm. It was firmer than normal. The capsule was tense and blue. The organ lacked attachment to the inferior diaphragmatic surface above (phrenicolienal ligament). It was bent on itself to about a right angle, the apex of the angle being at the midportion of the convex surface. Here, there was a transverse fissure 3.5 cm. in length and 0.8 cm. in depth. A point 0.5 cm. in front of its anterior end was the seat of a superficial rupture (possibly through a small vessel) which was 0.3 cm. long. It bled freely on slight pressure on the surrounding tissue and was surrounded by a recent blood clot. The hilus contained a smooth-surfaced, bluish, well defined mass, which was soft and rubbery, measured 5 cm. in diameter and was somewhat irregular; it could not be dissociated from the body of the organ. The mass was covered by large, moderately firm adherent clots. It consisted of thrombosed, dilated hilar veins, surrounded by edematous hemorrhagic tissue. The thrombi were lamellated, extending for a short distance into the intraperitoneal vessels and for 2 cm. into the main vessel, being softer, lighter red and of apparently more recent origin in the latter location. The intima of all branches was smooth and glistening; the thrombi were nowhere adherent to it. The splenic artery coursed through the mass, its lumen and those of its branches being patent throughout. The parenchyma presented a picture of extreme congestion, none of the gross structure ordinarily seen being recognizable. The splenic flexure of the colon had numerous fibrinous adhesions to the lateral abdominal wall. The body and tail of the pancreas from just to the left of the midportion were only loosely attached to the posterior abdominal wall by a mesentery-like fold of areolar tissue. This part of the pancreas was easily mobile but was not twisted or displaced. Posteriorly, this portion of the pancreas was covered by a smooth, glistening surface. More laterally toward the right, this surface disappeared, as did the loose mesentery-like structure of areolar tissue, as the posterior pancreatic surface

became densely adherent to the posterior abdominal wall. Toward the spleen, the tail of the pancreas became loosely attached to the spleen just below the hilus, the posterior pancreatic mesentery being lost in the densely hemorrhage-infiltrated tissue that surrounded the hilus. The spleen was loosely adherent to the splenic flexure, but no distinct ligamentous connection could be ascertained because of the extensive hemorrhage. The gastrosplenic ligament was heavily infiltrated with dark red clotted blood, and a similar infiltration covered the left lateral anterior surface of the pancreas. The omental bursa was devoid of blood and showed no gross anatomic changes; the foramen of Winslow was patent.

The rest of the autopsy showed nothing particularly abnormal. All the viscera were extremely pale and bloodless.

Microscopy of the spleen showed all the sinuses extremely distended with masses of well preserved erythrocytes, in such huge numbers that the intervening pulp was almost nowhere apparent, being represented by a few lymphocytes. No other changes were noted. Microscopy of the remainder of the organs showed nothing but severe anemia.

The anatomicopathologic diagnosis was: (1) acute posthemorrhagic anemia of the viscera, (2) acute intraperitoneal hemorrhage, (3) shock and (4) spontaneous, nontraumatic rupture of the spleen, intrasplenic congestion and hemorrhage and recent thrombosis of the splenic vein, mechanical (torsional?) and static.

COMMENT

To understand the existing relations in the abdominal viscera in this case, it is necessary to review briefly the embryology of the spleen and pancreas and the disposition of the peritoneal folds as they change from the embryonic state to that found in adult life. Originally the peritoneum leaves the posterior abdominal wall in the midline and passes forward to encircle the vertically lying stomach as a double-layered mesentery, the dorsal mesogastrium. As the stomach becomes rotated toward the right and horizontad (its left lateral surface becomes its adult anterior surface, while the right lateral surface becomes its adult posterior surface), the dorsal mesogastrium is pulled toward the left. This process, coupled with the great overgrowth and redundancy of the dorsal mesogastrium, causes it to assume a U-shaped appearance, the hollow of the U facing toward the right behind the stomach, the hollow being the precursor of the adult lesser sac. Within the loose areolar tissue of the dorsal mesogastrium and between its two layers at or near the point of greatest convexity, the splenic anlage develops. It is at first entirely invested on all surfaces by peritoneum. By adhesion later of parietal peritoneal surfaces as the lateral bending of the dorsal mesogastrium continues, the peritoneal investment of the spleen leaves it at the hilus and passes over to the lateral border of the kidney. This reflection is brought about by the adhesion of the ventral peritoneal layer of the dorsal mesogastrium (originally its right leaf) to the posterior abdominal wall to form the dorsal surface of the retrogastric space, the left leaf of the dorsal mesogastrium, by its adhesion to the parietal peritoneum over the kidney and diaphragm, forming the adult

lienorenal and lienophrenic ligaments. At these points of adhesion, firm strands of connective tissue later develop between the serous surfaces. By adhesion of the dorsal mesogastrium to the splenic flexure, the colicolienal ligament is formed in similar manner, while similar adhesion of the dorsal mesogastrium to the great omentum, transverse mesocolon and phrenic parietal peritoneum just caudad to the spleen forms the colicophrenic and costocolic supporting ligaments of the spleen. These changes occur during the second half of intra-uterine life.

Meanwhile, the pancreas has begun as an outbudding from the definitive duodenal portion of the embryonic intestine, pushing its way between the layers of the mesoduodenum. It then turns cephalad, pushing its way between the layers of the dorsal mesogastrium by the displacement of which, occasioned by the gastric rotation, it is brought backward against the posterior abdominal wall. At this juncture, its original posterior peritoneal investment, the reduplication of the original left lateral leaf of the dorsal mesogastrium, becomes adherent to and fused with that fold of dorsal mesogastrium reduplicated from the left lateral leaf and previously adherent to the posterior parietal peritoneum. The pancreas thus becomes fixed and virtually extraperitoneal, and the main splenic vessels, originally situated between two peritoneal layers in front of the pancreas, now, through the interposition of this organ and the subsequent fusion of the posterior peritoneal investment of this organ, is covered by peritoneum only anteriorly (Huntington [34]).

If, therefore, this fusion, for whatever reason, fails to develop properly and completely, the pancreas in whole or in part remains, as it originally was, an intraperitoneal organ, and the usual splenic supporting ligaments fail to develop. Of these, the lienophrenic and the lienorenal ligament are probably the most easily affected, since it is in this lateral region that disturbances of adhesion of peritoneal surfaces would be occasioned by the neighboring pancreas. Situated as the pancreas is, posteriorly and rather remotely, the colicophrenic and the costocolic ligament are less apt to be disturbed in formation. Besides, these two structures are not intimately connected with or are not a part of the spleen and its investments and hence cannot limit its motion by tension. Directly they cannot limit its mobility except by resisting its advance in their direction, a force of doubtful importance when their thin elastic structure is considered.

That such must have been the state of affairs in this case is suggested by the loosely adherent attachment of the pancreas to the posterior abdominal wall, its attachment to the spleen and the presence of a rudimentary posterior pancreatic mesentery. This suggestion is further

34. Huntington, G. S.: The Anatomy of the Human Peritoneum and Abdominal Cavity from the Standpoint of Development and Comparative Anatomy, Philadelphia, Lea Bros. & Co., 1903.

strengthened by the absence of any semblance of a lienophrenic ligament. Such conditions, therefore, deprived the spleen of its major supports and afforded it greater mobility. It remained, however, as developmentally it must, closely connected with the stomach by the gastrosplenic ligament. With its physiologic mobility during digestion, hunger and other unusual causes, it is possible that the stomach, in its contractions, pulled the unchecked and unsupported spleen into unusual positions, causing recurrent, albeit temporary, passive congestion. It is not improbable to conceive of an excessive force so distorting the position of the spleen as to cause the congestion to become sufficient, especially if lasting for some time, to occasion subcapsular hemorrhage and subsequent capsular rupture, with the resulting clinical picture. In this connection, it must be remembered that the splenic circulation is an open one [35] and that it is therefore more liable to subcapsular hemorrhage. Alternatively, it may be that the recurrent displacement of the spleen, with the resulting changes in the course of the splenic vessels, especially at or near the hilus, produced a gradual thrombosis of the more labile vessel, the splenic vein. This may so have narrowed the venous lumen that a sudden excessive distortion brought about by a more extreme change in position may have caused a pronounced passive congestion, with subsequent subcapsular hemorrhage and capsular rupture. The recurrent abdominal pain and the at first gradual, then rapid, development of abdominal signs and symptoms, suggest that the process was not continuous but intermittent, the first phase being due to subcapsular hemorrhage, and the second, or shock, phase, to the capsular rupture and intraperitoneal hemorrhage. It is not necessary to assume, as is so frequently done with hemorrhages into ovarian cysts that are not of endometriotic origin, that the pedicle had been twisted, the hemorrhage brought about, and, before laparotomy or autopsy, the pedicle had become untwisted. In an organ the position of which is closely delimited and the vessels of which are rather rigidly fixed by surrounding tissues, positional changes less than pedicle torsion may be sufficient to slow the circulation and cause intraparenchymal congestion and hemorrhage, as was found in this case.

From the clinical and pathologic pictures, it is probable that some intra-abdominal (gastro-intestinal?) physiologic upset, with altered dynamic relations of the viscera, caused a partial recurring torsion of the spleen, with resulting thrombosis of the splenic vein and splenic parenchymal congestion of an extreme grade, which finally led to rupture, shock and death. The absence of the diaphragmaticolienal ligament and its reflection of the abdominal wall, the chief supports of the spleen

35. Maximow, A. A., and Bloom, W. A.: A Textbook of Histology, ed. 2, Philadelphia, W. B. Saunders Company, 1934.

(these are absent rarely—less than 2 per cent together [36]), make this theory likely. Furthermore, the attachment of the splenic flexure of the large intestine and the upper part of the descending colon, together with the loose mesenteric attachments of the latter, suggest that the spleen may have been moved mechanically with them in some colonic physiologic disturbance.

Spontaneous splenic rupture is important from the medicolegal point of view. It is a well known fact that traumatic injuries of abdominal viscera may occur without external signs, cutaneous or muscular, of the inciting trauma.[37] Under such circumstances, a surgeon finding a ruptured spleen may be called on to attest its traumatic character.[4] As we have pointed out, however, there exist genuine cases of nontraumatic, spontaneous splenic rupture. Such testimony must, therefore, be given with caution and only when a clearcut history of trauma is obtained.

CLINICAL FEATURES

An analysis of the clinical features of these cases reveals some interesting facts:

1. Sex apparently plays no part in the picture. In the twenty-one genuine and seven dubious cases reviewed, the rupture occurred sixteen times in males and twelve times in females.

2. Age appears to play no part. The condition occurred twice in persons under 20 years of age, seven times in those between 20 and 30, six times in those between 30 and 40, seven times in those between 40 and 50 and five times in those between 50 and 60. The condition appears to be fairly evenly distributed throughout the various age periods.

3. In five of the cases in which no intrinsic lesions of the stomach or gallbladder could be detected there was a well established history of epigastric distress related to meals.

4. In five cases the onset of attack occurred shortly after eating or drinking.

5. The site of rupture was extremely variable, showing no decided predilection for any site. The lower and upper poles, the convex and concave surfaces, the hilus and the splenic notch were involved with equal frequency.

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36. Cunningham, D. J.: Text-Book of Anatomy, ed. 5, New York, William Wood & Company, 1923. Huntington.[34]

37. Vance, B. M.: Subcutaneous Injuries of the Abdominal Viscera: Anatomic and Clinical Characteristics, Arch. Surg. **16**:631 (March) 1928.

6. Vomiting occurred in only twelve of the cases. (Trendelenburg [38] claimed that this is a constant sign in rupture of the spleen.)

7. Shock occurred in only fifteen cases.

8. Pain in the left shoulder, although supposed to be pathognomonic of splenic rupture, occurred in only three cases. Pain in the right shoulder occurred in only one case.

SUMMARY

A case of spontaneous rupture of a normal spleen is reported. The embryogenesis of the spleen and its peritoneal supports is reviewed. The physiologic and anatomic conditions making possible spontaneous rupture are described and discussed. The literature is critically reviewed; reports of twenty genuine cases and seven questionable cases are collected. Some interesting clinical features are noted.

It is suggested that future cases be studied carefully from the point of view of physiologic dynamics of the abdominal cavity and the anatomic relations of the splenic and pancreatic peritoneal reflections.

The medicolegal significance of this condition is pointed out.

Dr. Benjamin Kogut, attending surgeon at the Beth-El Hospital, gave us permission to use the clinical data in the case reported here.

38. Trendelenburg, in discussion on Finsterer, H.: Zur Diagnose und Therapie der stumpfen Bauchverletzungen, Wien. med. Wchnschr. **68**:1217, 1918.

PRURITUS ANI

HISTOLOGIC PICTURE IN FORTY-THREE CASES

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Seldom may one find a disease so little understood as pruritus ani. There is great dissension in regard to its cause. The variety of remedies which have been offered proves that nothing has been produced resembling a cure.

DIRECT AND INDIRECT PRURITUS

Montague [1] distinguished two types of pruritus, direct and indirect. The latter is called by others essential or idiopathic pruritus.

In the direct type of pruritus, local anal diseases such as fistulas, fissures, ulceration of the anus and rectum, polyps, papillae and hemorrhoids have been given as causes. In the indirect type of pruritus, Montague regarded the itching as a referred sensation caused by disorders in distant organs, i. e., the stomach, gallbladder and appendix and other organs. Montague expressed the belief that whenever a viscus is the seat of a disease a stream of afferent stimuli is generated and transmitted to the central nervous system. The irritant stimulus is referred, not to its true source, but to the skin of the anal region.

Bacteria and fungi, pediculi and pin worms have been mentioned frequently as etiologic factors. Various constitutional disorders, such as uremia, gout, diabetes and rheumatism, have been blamed for the production of pruritus. In a certain percentage of cases the condition has been attributed to allergy.

In the face of all these divergent theories, it may be truthfully said that the etiology of this distressing condition is not known.

About thirteen years ago, Lockhart-Mummery [2] wrote that histologic examination of pruritic skin may solve some day the mystery of pruritus ani. In the literature we could, however, find only two such studies. Montague,[1] in his book on pruritus, described an acute or subacute

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From the Department of Surgery and Pathology, St. Francis Hospital.

1. Montague, J. F.: Pruritus of the Perineum, New York, Paul B. Hoeber, Inc., 1924.

2. Lockhart-Mummery, L.: Diseases of the Rectum and Colon, New York, William Wood & Company, 1923.

exudative dermatitis, with lichenification and kraurosis as possible end-results. In Buie's book,[3] Montgomery reported the results of histologic study in five cases of pruritus ani. He expressed the belief that the changes in the skin in cases of pruritis ani correspond closely to those seen in cases of neurodermatitis.

MATERIAL

Our present paper is based on the clinical and histologic studies of 43 cases of anal pruritus, which were found among 386 patients with conditions of the rectum—an incidence of 11 per cent. There were 22 men and 21 women. No Negroes were in the group. While Montague [1] expressed the belief that there is no racial predisposition in pruritus ani, Taussig [4] pointed out that he had hardly ever seen a Negress with pruritus.

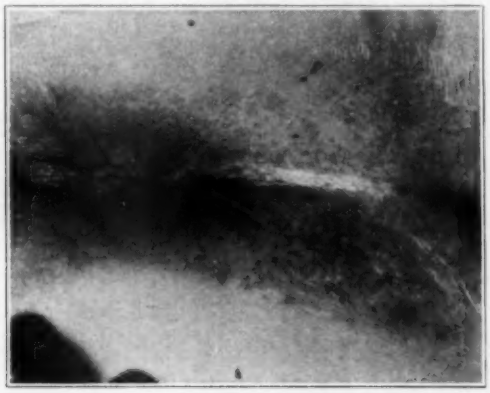

Fig. 1.—First stage of pruritus of a few weeks' duration. There are redness and swelling of the skin, not only around the anus but also in the area extending to the coccyx.

No children were observed with true pruritus. Our youngest patient was 24 years old, and the oldest, a woman, was 76 years old. The average age of the men was 45.1 years, and of the women, 37.4 years.

ANAL LESIONS IN PRURITUS ANI

In our cases we made a histologic study of not only the specimens removed from the pruritic zone, but also every surgical specimen obtained from the anal canal. We hoped that the anal canals of patients with pruritus might differ from those of patients without pruritus. The great majority of our patients with pruritus presented one or more pathologic conditions in the anal canal. They were, in the order of

3. Montgomery, in Buie, L. A.: Proctoscopic Examination and the Treatment of Hemorrhoids and Anal Pruritus, Philadelphia, W. B. Saunders Company, 1931.

4. Taussig, F. J.: Leukoplakic Vulvitis and Cancer of the Vulva, Am. J. Obst. & Gynec. **18**:472, 1929.

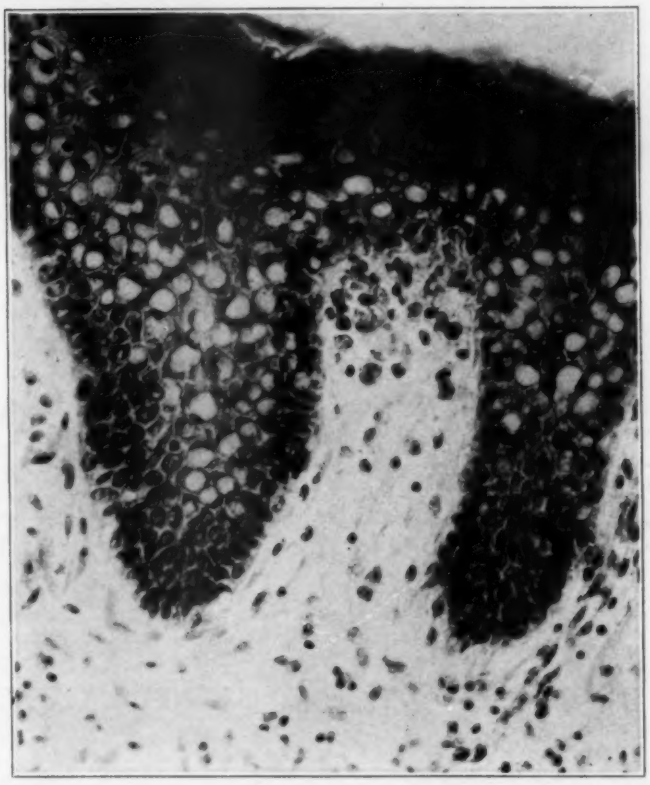

Fig. 2.—Intra-epithelial edema in the first stage of pruritus.

Fig. 3.—First stage of pruritus with vesicle formation.

frequency: hemorrhoids, infection of the anal ducts, inflammation and hypertrophy of the papillae, fissures and fistulas.

By special nerve stains, our attention was attracted to a large number of myelinated nerves which were running to the tip of the anal papillae, at the mucocutaneous line. In the tip of the anal papillae, almost without exception, Meissner's tactile corpuscles were found lying beneath the epithelium. The presence of these tactile bodies explains the extreme sensitivity of the anal papillae. It is possible that inflammations, which are so common near the mucocutaneous line, irritate these nerve corpuscles and thus produce the sensation of itching.

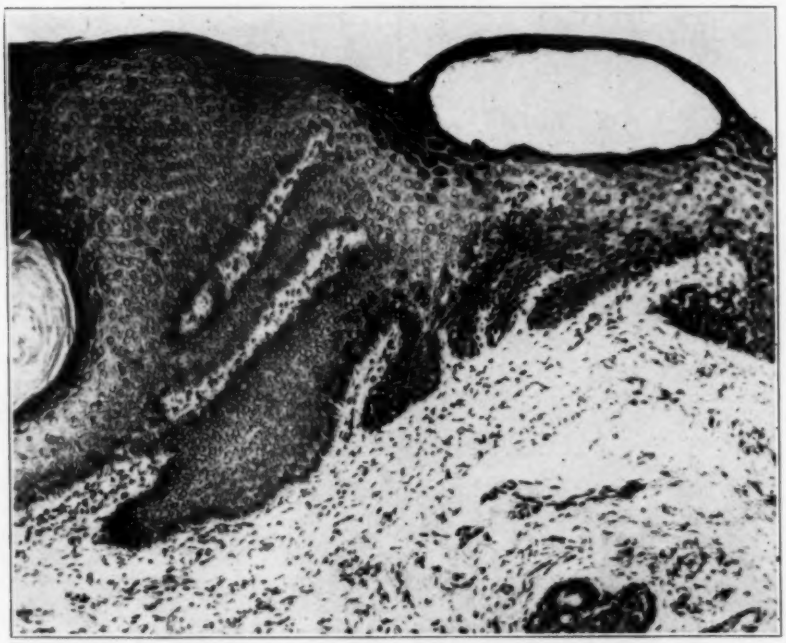

Fig. 4.—Photomicrograph of the lesion in figure 3. A vesicle is shown in the epidermis.

Histologic study, however, of surgical specimens removed from the 343 patients without pruritus revealed that the pathologic picture of the anal canal of a patient with pruritus was not different from that of the anal canal of a patient without pruritus. Therefore anal lesions cannot be regarded as the essential cause of pruritus. This would conform with our clinical experience. Follow-up studies which we made in our series of cases revealed that radical removal of all anal lesions often will improve the condition of the patient markedly, but seldom will bring about a complete cure.

HISTOPATHOLOGIC PICTURE OF THE SKIN IN PRURITUS ANI

The cutaneous changes found in our 43 cases differed according to the duration of the pruritus. Our youngest patient, a 27 year old woman, complained of severest itching for five months; our oldest patient had symptoms for thirty-five years. While different histologic pictures may be present in the same specimen of skin, we believe, never-

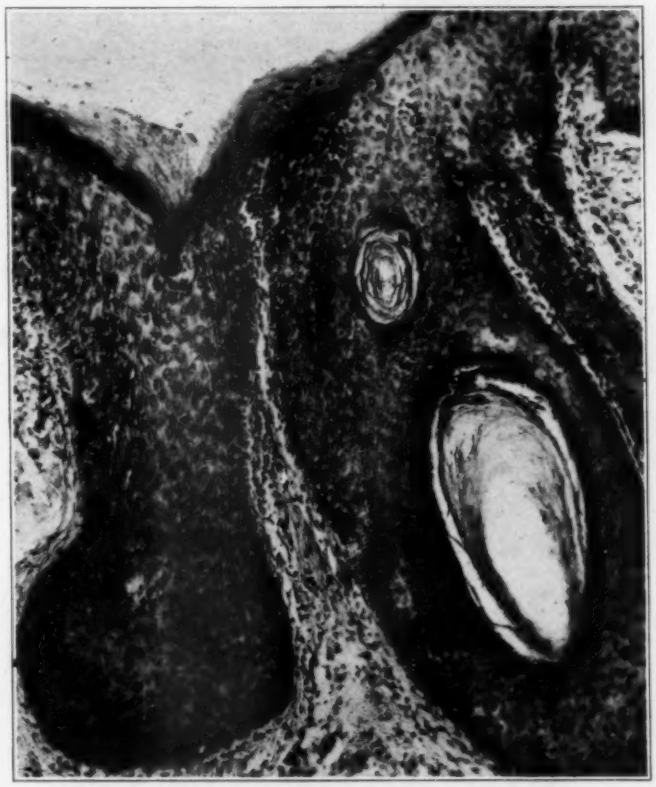

Fig. 5.—Second stage of pruritus. There are marked proliferation of the malpighian layer, and horny plugs in the hair follicle. The cells are undifferentiated.

theless, that pruritus ani runs a typical course, and we had no difficulty in classifying the cutaneous changes into four stages.

The first stage of pruritus shows evidence of exudative inflammation. The cells of the malpighian layer are markedly swollen, the structure of the protoplasm is entirely destroyed and a large clear space is found. The nucleus is compressed and pushed to the periphery of the cell body. It has the shape of a half-moon. The intercellular bridges are not recognizable. In the corium, dilatation of blood and lymph vessels is evident, and there is perivascular infiltration with lymphocytes, plasma

Fig. 6.—Second stage of pruritus. There is hyperkeratosis of the surface epithelium.

Fig. 7.—Third stage of pruritus. The skin is thin and dry and without hair and pigment.

cells and occasional leukocytes. In a few cases exudate has collected in the upper layers of the epidermis and may form vesicles protruding over the surface.

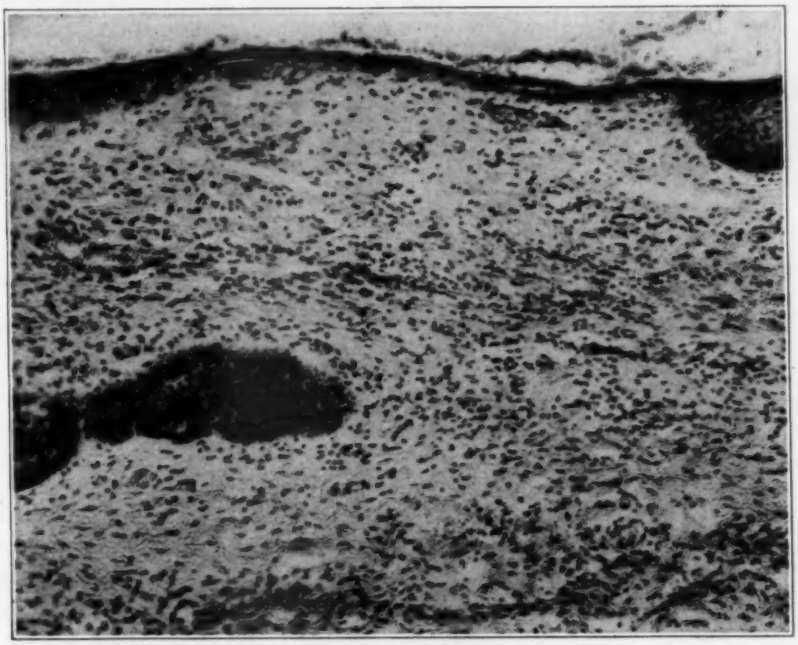

Fig. 8.—Third stage of pruritus. There are marked atrophy of the surface epithelium and the sebaceous glands and loss of hair.

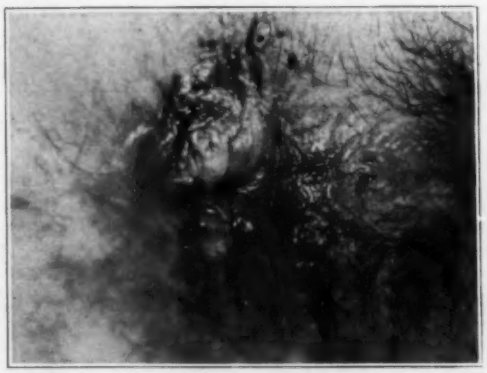

Fig. 9.—Fourth stage of pruritus. Torpid ulcers are seen in the atrophic skin surrounding the anus.

The second stage of pruritus is characterized by epithelial hyperplasia. There is marked thickening of the epidermis. The rete pegs

are elongated and separated by narrow papillary bodies. The cells of the malpighian layer are deeply stained; they appear unripe and less differentiated than in normal skin. Often mitotic figures are present. In many cases the epidermal cells form either branching strands, growing into the corium or broad cell masses obliterating the papillary bodies. Marked cellular proliferation is also observed in the walls of hair follicles. Strands of young, undifferentiated cells are growing from the outer sheaths of hair follicles into the surrounding connective tissue. In many instances these proliferative areas have a definitely atypical appearance.

Fig. 10.—Section of pruritic skin with an ulcer. There is absence of a vigorous defense reaction.

The stratum corneum of the epidermis is also much thicker than normal. The ostium of hair follicles is plugged with hornified material. The same material is found in the ducts of sebaceous glands.

In the third stage of pruritus, atrophy of the epidermis and especially of the hair follicles and sebaceous glands is found. The surface epithelium is only a few cell layers thick, the hair follicles are distended by horny plugs and the sebaceous glands either are completely missing or consist only of undifferentiated cells which do not show evidence of secretory activity.

The fourth stage of pruritus is characterized by multiple epithelial defects. Excoriations, deep fissures and shallow ulcers are found. In some epithelial defects, leukocytic infiltration and marked edema are observed, apparently due to secondary bacterial invasion; more often, however, no vigorous defense reaction of the tissue is recognizable, and most of the ulcers look torpid.

Our observations coincide, in the main, with Montague's and especially with Montgomery's descriptions. Pruritus ani has, in our opinion, a definite histologic picture. Never have we seen these cutaneous changes in patients with disease of the rectum without pruritus.

COMMENT

Does the histologic picture of pruritus ani throw some light on the etiology of this condition? There is nothing in our observations which would suggest a bacterial or parasitic cause. We shall not deny that certain bacteria or fungi may complicate pruritus, but in the early stages in our cases no histologic evidence of bacterial or parasitic infection was present. Neither were the results of our microscopic examinations in harmony with the theory that pruritus is an allergic disease; and the neurogenic theory of pruritus also seems unwarranted in the light of our observations. We feel, furthermore, justified in disagreeing with those who believe that inflammatory lesions of the anal canal and hemorrhoids are responsible for pruritus. There was no difference between the pathologic picture of the anal canals of persons with pruritus and that of persons without pruritus.

In studying the cutaneous changes in cases of pruritus ani, we were reminded again and again of the histologic pictures described in cases of chemical dermatitis. Hydrops of the epidermis cells, irregular proliferation of the stratum mucosum and of the hair follicles, hyperkeratosis with plugging of the hair follicles and atrophy of the sebaceous glands are changes characteristic of dermatitis due to chemical irritants. The four stages which we have seen in pruritus i. e., (1) exudative inflammation, (2) epidermoid proliferation, (3) atrophy of the epidermis and sebaceous glands and (4) epithelial defects, can be produced in the skin of rabbits and mice by certain chemical substances which, in various pathologic conditions, are present in the human feces. We believe that besides other hydrocarbons, skatole may be the responsible agent, because Stoeber and Wacker [5] were able, by the injection of skatole into the rabbit, to produce the same cutaneous changes which we have described in pruritus.

5. Stoeber, H., and Wacker, L.: Ein weiterer Beitrag zur Erzeugung atypischer Epithelwucherungen mit Eiweissfaeulnisprodukten, München. med. Wchnschr. **57**:947, 1910.

Skatole, a methyl indole, is a derivative of protein and is formed in the intestines from tryptophan by the action of anaerobic bacteria. While skatole is absent in the stool of healthy children and also in the stool of most adults, Herter [6] found excessive amounts in the feces of patients suffering from mental despression and anemia and especially from chronic intestinal disorders. These conditions are, according to Montague, often associated with pruritus. In healthy children, on the other hand, true pruritus is unknown.

SUMMARY

The histologic picture in 43 cases of pruritus is not in accord with the theory that bacterial or fungus infection is the cause of pruritus. Allergy and neurogenic factors can also be excluded as etiologic factors in the light of our microscopic observations. The results of our studies suggest as the underlying cause of pruritus ani a chemical dermatitis. In pathologic conditions, the human feces contain substances which are known to produce the same cutaneous changes which we have observed in pruritus.

Follow-up studies which we made in our cases of pruritus revealed that radical removal of all lesions in the anal canal will improve the condition of the patient but will not bring about a complete cure. There is no difference between the pathologic picture of the anal canals of patients with pruritus and that of patients without pruritus. Anal lesions cannot be regarded as the esential cause of pruritus.

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6. Herter, C. A.: The Occurrence of Skatole in the Human Intestines, J. Biol. Chem. **4**:101, 1908.

REFLEX DYSTROPHY OF THE EXTREMITIES

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The proper nutrition of adult tissue is the result of a balance between anabolic, or constructive, metabolic activities and catabolic, or destructive, metabolic activities. Wear and tear are replaced by repair. Injury is followed by regeneration. The forces which accomplish such an equilibrium are incompletely understood. A study of patients, therefore, in whom this balance has been disturbed is of some interest, as it may throw light on the normal control of the nutrition of tissue.

After mild trauma, usually a blunt injury affecting a wide surface or a low grade infection of traumatic or nontraumatic origin, partial injury to a nerve, frost-bite or a burn, there occurs occasionally a peculiar vasomotor and trophic disturbance which has been designated by a variety of names, depending on the outstanding symptom, such as acute atrophy of the bone,[1] traumatic angiospasm,[2] traumatic vasospasm,[3] chronic traumatic edema,[4] peripheral acute trophoneurosis,[5] reflex nervous atrophy,[5] reflex nervous dystrophy [6] and posttraumatic osteoporosis.[7] Obviously the authors have focused their attention on different manifestations of the same syndrome. The vasomotor disturbance, while prominent at first, may later be overshadowed by trophic changes. A hard, nonpitting edema is only one symptom and is sometimes hardly

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From the Department of Surgery, University of Illinois, College of Medicine, and St. Luke's Hospital.

1. (*a*) Sudeck, P.: Ueber die akute entzündliche Knochenatrophie, Arch. f. klin. Chir. **62**:147, 1900. (*b*) Noble, T., and Hauser, E.: Acute Bone Atrophy, Arch. Surg. **12**:75 (Jan.) 1926. (*c*) Gurd, Fraser B.: Posttraumatic Acute Bone Atrophy, Ann. Surg. **99**:449, 1934; Arch. Surg. **32**:273 (Feb.) 1936.

2. Morton, J. J., and Scott, W. J. M.: Some Angiospastic Syndromes in Extremities, Ann. Surg. **94**:839, 1931.

3. Lehman, E. P.: Traumatic Vasospasm, Arch. Surg. **29**:92 (July) 1934.

4. (*a*) Klassen, P.: Ueber das chronische traumatische Handrückenödem, Monatschr. f. Unfallh. **36**:289, 1929. (*b*) Brauecker, W.: Das traumatische Oedem, ibid. **38**:241, 1931; (*c*) Pathogenese und Therapie des traumatischen Oedems, Arch. f. orthop. u. Unfall-Chir. **32**:577, 1933. (*d*) Bettmann, E., Jr.: Ueber das traumatische harte Oedem des Handrückens, ibid. **32**:570, 1933.

5. Zur Verth, M.: Periphere akute Trophoneurose der Hand, Monatschr. f. Unfallh. **30**:309, 1929.

6. Sudeck, P.: Die trophische Extremitätenstörung durch periphere (infektiöse und traumatische) Reize, Deutsche Ztschr. f. Chir. **234**:596, 1931.

7. Fontaine, R., and Herrmann, L.: Posttraumatic Osteoporosis, Ann. Surg. **97**:26, 1933.

noticeable. The osteoporosis, if systematically looked for, is often found; it should be distinguished from atrophy due to inactivity by its sudden appearance after trauma, by its spotty distribution and by the accompanying pain and vasomotor disturbance.

After the acute symptoms of a comparatively mild injury, often without damage to bones, tendons or larger vessels, have subsided, there appears a hard, nonpitting edema which is frequently accompanied by paroxysms of pain. The skin is glossy with a bluish tint, and the extremity is sensitive to draughts, to changes in temperature and to superficial and deep pressure. Sensory disturbances are indefinite; there is often a glovelike hypo-esthesia which does not follow any sensory nerve distribution. The muscles at first are hypertonic, owing to an increased reflex irritability, but later become atonic. Their electric excitability is diminished, although of normal quality. The temperature of the skin is first higher and later lower than that of the unaffected extremity; there is profuse sweating. Sometimes an increased growth of hair or a weeping eczema appears. The nails become brittle and ribbed. The bone shows a characteristic spotty atrophy, which may later become diffuse; the growing bone may be retarded in its growth, the epiphysial lines closing prematurely. The capsules of the joints shrink; movement of such joints is very painful, and mobilization of such contractures aggravates the condition. Weir Mitchell's classic description of causalgia closely resembles this picture.[8]

An oscillometric study of the peripheral circulation reveals first an increase and later a decrease in the height of the oscillometric curve. The minute vessels are less responsive to cold; the hyperemic reaction to cold appears much slower and lasts longer. This is an abnormal vasomotor response which in turn may result in the metabolic "trophic" disorders.

Histologic sections taken from such extremities reveal edema of the subcutis, with a shrinkage of fat, areas of minute hemorrhages and perivascular infiltrations. The latter was the outstanding feature in Lehman's cases of traumatic vasospasm.[8] The bone in acute reflex dystrophies has been studied by Vialleton,[8a] Fontaine and Herrmann[7]

8. Mitchell, S. W.; Morehouse, G. R., and Keen, W. W.: Gunshot Wounds and Other Injuries of Nerves, Philadelphia, J. B. Lippincott Company, 1864. "Causalgic pain differs from the pain of peripheral neuritis. Outstanding feature is burning, intensified by warmth and dependent position. Stroking, manipulation, exercise accentuate it. Fright, unexpected noise, anxiety bring on a paroxysm. Hyperesthesia, wasting of tissues, atrophy of muscle and decalcification of phalanges are seen; the latter occurs when vasodilatation in the bone is present. Temperature regulation is poor; in a cool room the hand is mottled and blue; in a warm room or bath the hands feel acutely inflamed, resembling a chilblain."

8a. Vialleton, cited by Gurd.[1c]

and Rieder [9]; they found an apposition of osteoid tissue without calcification and a spotty distribution entirely unlike any other type of atrophy of the bone.

This syndrome, if looked for, occurs not infrequently but gradually subsides; it may become, however, so intractable that a long-drawn-out disability of from 35 to 100 per cent results.[10] Occasionally the arm has to be amputated, but the pain persists in the stump and radiates to the neck and shoulder. In patients in whom these symptoms and signs occur in their full intensity, a constitutional inferiority is often unmistakable. Their emotional upsets aggravate the picture.

Reflex dystrophy is often mistaken for atrophy of disuse, for artificial edema, for anxiety neurosis or for malingering. It must be differentiated from venous and lymphatic edema, from inflammatory reactions occurring around carpal and metacarpal fractures, from tuberculous or pyogenic osteomyelitis and from infection of the tendon sheaths and fascial spaces. On the lower extremity spasmodic flatfoot may simulate this condition.

The important feature of this peculiar disturbance of tissue metabolism is that an exaggeration of a nutritional reflex, which is set up by the initial injury or infection, does not subside when the effects of trauma or infection have been overcome but becomes a fixed, self-perpetuating mechanism in which the catabolic (destructive) activities are predominating. Thus the atrophy of skin, subcutis and bone may be regarded as an active process.[6] This nutritional reflex has been described and analyzed from the physiologic standpoint by Hess.[11] Its adequate stimuli seem to be products of metabolism—products of digestion.

REPORT OF CASES

CASE 1.—Julia G., an 18 year old Italian girl, referred by Dr. Eric Oldberg, sustained an injury to the right wrist in an electric wringer. No fracture and no rupture of tendons or injury to large vessels occurred, but a swelling of the wrist and dorsum of the hand developed. This was treated by heat, massage and diathermy, but instead of subsiding it became definitely worse. The pain which was originally localized at the wrist, affected the fingers, which became stiff and swollen; it also traveled up to the elbow with shooting paroxysmal pain to the shoulder and the right side of the neck. The girl was highly emotional and querulous and was seeking compensation from her employer. When she was first seen, seven months after the injury, there was a hard, nonpitting edema of the dorsum of the hand extending slightly above the wrist. The fingers were stiff and were held in an extended position. The skin was glossy and moist, and the

9. Rieder, William: Das histologische Bild der akuten Knochendystrophie, Arch. f. klin. Chir. **177**:400, 1933.

10. Klassen.[4a] Zur Verth.[5]

11. Hess, W. R.: Die Regulierung des Blutkreislaufes, Leipzig, Georg Thieme, 1930.

slightest draught or immersion into water of 15 C. would produce a cyanotic hue; and the patient would shriek with pain and weep. There was no evidence of injury to bones, tendons or vessels. A roentgenogram of the hand revealed diffuse atrophy, as in a late stage of traumatic osteoporosis.

The patient's mental age was 11; the intelligence quotient was 71 by the Simon-Binet test. She was rated as having a borderline mental deficiency (Miss E. Schultz). Neurologic examination by Drs. G. W. Hall and R. P. Mackay revealed no motor, sensory or reflex disturbance in the affected extremity but a definite "state of mind," an anxiety hysteria, with exaggeration of all symptoms.

Injection of 2 per cent procaine hydrochloride to the stellate and second thoracic ganglions relieved the vasomotor phenomena and stopped the pain. It was explained to the patient that first a minor operation would be performed at the wrist and should this fail to relieve the symptoms, a major operation would be performed at the neck. Accordingly, the median nerve and the ulnar and radial arteries were stripped of their sheaths. The median nerve was surrounded by a fine layer of hyperemic connective tissue. After operation the pain subsided, and physical therapy could be started without causing pain. All symptoms except the pain in the shoulder and in the cervical region disappeared. The patient's state of mind improved. Three months after the operation she admitted that she had regained the use of her hand. The pain along the brachial plexus had improved. She was again encouraged and told that a further operation, namely, cervicothoracic ganglionectomy, would relieve the pain if that seemed to persist. Six months after the operation she reported complete recovery.

The important factors operating in this case were: (1) a constitutional inferiority manifested by the patient's low mental age and low intelligence quotient; (2) an unsuitable environment, the patient being urged by her mother and a lawyer to obtain maximal benefits from the injury, and (3) a definite reflex dystrophy, originating at the site of injury around the median nerve, which could be interrupted by removal of the irritating focus and a partial periarterial sympathectomy. The condition in this case could readily be called causalgia.

CASE 2.—J. H., a 41 year old unmarried woman, had received radium therapy and had undergone dilation and curettage at the Mayo Clinic in 1932 for menorrhagia. Six months later hysterectomy and ovariectomy on the right side were done in Cleveland for multiple fibroid tumors. Both after the insertion of radium and after the hysterectomy there occurred an attack of pain in the right groin, with a swelling of the thigh, which was diagnosed as thrombosis of the external iliac vein. The patient stayed in bed for four months with considerable pain. There was no elevation of temperature. On her admission to St. Luke's Hospital on Aug. 4, 1935, there were no abnormal findings except those referable to the right lower extremity. There were unilateral vasospasm extending from the toes to the groin, a peculiar paresthesia of the stocking type which did not follow any peripheral nerve and sensitivity to heat and cold. The patient hesitated to put weight on the limb and walked on crutches. The limb was atrophic, there being a difference of 1 inch (2.5 cm.) in circumference 6 inches (15.3 cm.) below the knee. The skin was scaly, and the muscles were flaccid. Neurologic examination by Dr. R. P. Mackay revealed nothing abnormal in the central nervous system and an "old maid" personality, but not enough to cause any trouble. The patient had a definite mother and brother fixation and stated that she had no heterosexual feelings. The pain was not considered hysterical.

A paravertebral injection of procaine hydrochloride into the second, third and fourth lumbar segments resulted in a complete sympathetic paralysis of the right lower extremity. It abolished the difference in temperature and produced a dry skin. All movements, including hyperextension of the knee and thigh, were free and painless (fig. 1).

Roentgen examination revealed spina bifida occulta at the top of the sacrum. To rule out the possibility of a urinary obstruction causing the pain, an intra-

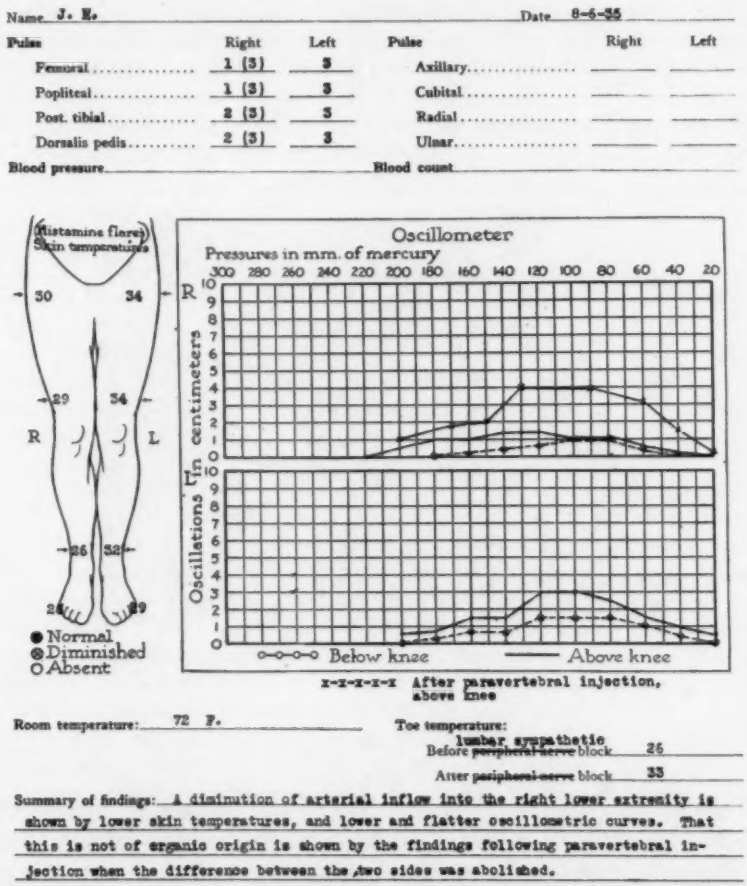

Fig. 1.—Circulatory record of J. H. After paravertebral injection the difference in pulse rate, skin temperature and oscillometric curves was abolished, indicating a central or reflectoric sympathetic stimulation.

venous pyelogram was made, with completely negative results. The basal metabolic rate was minus 2 per cent. The sedimentation rate was within normal limits, indicating the absence of even a latent phlebitis. The blood count was normal. On August 26 the right iliac vessels were explored through an anterolateral extraperitoneal incision. Dense fibrous tissue was found around the external iliac vessels, chiefly encasing the vein. The vessels were completely stripped of this tissue, which contained enlarged lymph glands.

The convalescence was uneventful. The histologic study of the removed tissue revealed small lymph nodes with a moderate hyperplasia of the mononuclear cells and fibrous tissue around the glands (Dr. E. F. Hirsch).

The patient was reexamined two weeks, four weeks and three months after operation. The pain, paresthesia and sensitivity to cold disappeared. She had used the leg freely without crutches and rode horseback ten weeks after the operation with no return of symptoms. The leg increased in size, there being only a ¼ inch (0.6 cm.) difference in the circumference of the calf 6 inches below the knee. There was no cyanosis in the dependent position and no pain on walking. The oscillometric curves and skin temperatures were identical for the two limbs. Five months after the operation the patient reported complete recovery.

The case was interpreted as one of reflex dystrophy originating from a pelvic lymphangitis and periphlebitis, which in turn was activated by the insertion of radium. After the vein was stripped, the focus of irritation was disconnected from the cord.

Case 3.—Mrs. D. R. J., 25 years old, referred by Dr. Charles A. Elliott, was first seen on Sept. 2, 1935. Three years previously, after the normal delivery of a healthy boy, there gradually developed a painful cyanosis of the lower extremities. The skin became mottled. Paroxysms of pain would occur after exposure to cold or heat or even on standing. The skin became scaly and slightly atrophic. The feet were always cold. Repeated examinations by Dr. Hillis revealed normal pelvic organs. A pelvic thrombosis was suspected but could not be substantiated. Studies of the blood, including the platelet count, coagulation time, bleeding time and blood calcium determination, revealed normal figures. The basal metabolic rate was normal.

On physical examination the peculiar mottling of the skin was very definite. At certain places these cutaneous venules seemed thickened and nodular. During an examination at the Billings Hospital, Dr. Paul Bucy performed a biopsy of such a nodular vein and sent me the specimen for study. The histologic section of this vein revealed a cushion of intimal and subintimal tissue, the remnants of an old nodular phlebitis (Dr. Sol Rosenthal, University of Illinois).

A block of the second, third and fourth sympathetic ganglions with procaine hydrochloride temporarily abolished the coldness, perspiration and mottling. The limbs felt normal, without any evidence of other than sympathetic paralysis. Lumbar sympathectomy was advised, but has not been carried out so far.

In this instance the reflex dystrophy probably originated after childbirth from the nodular phlebitis, which may have had an infectious or a metabolic basis. The condition has been stationary for three years, and sympathectomy seems justifiable.

Case 4.—Mr. H. S., a 25 year old, well built, muscular man, was grinding the spark plugs of his car, when he was suddenly seized with pain in the right axilla, shooting into the right arm. The arm promptly began to swell. He went to bed and elevated the arm. The acute pain subsided, but there remained a permanent swelling of the arm and a deep boring pain after muscular exercise, accompanied with a widespread arterial flush. When he was seen eight months after the injury, the diagnosis of axillary thrombosis caused by effort was made. Outside of an obvious venous obstruction characterized by development of collateral channels over the chest (fig. 2), a lower oxygen content of the cubital vein on

the affected side and a block of the subclavian vein under the pectoral muscle visualized by an intravenous injection of skiodan (fig. 3), the patient presented a peculiar vasomotor instability of the affected arm. On muscular effort a widespread flare was visible. The oscillometric curves were higher on the affected side. There was a persistent edema, which was only slightly influenced by posture. On June 8, 1933, the subclavian vein was exposed on the anterior wall of the chest, below the pectoral muscles. It was found to be a fibrosed cord, surrounded by considerable perivenous adhesions. The artery was completely free and pulsated well. The vein was stripped from its adhesions for a distance of 4 cm. (1¾ inches). The vein was not resected, as a future recanalization was still thought to be possible. Immediately after the operation, the pain on exercise, the vasomotor instability and the edema subsided; although the venous obstruction had not been relieved. The patient has had no recurrence of symptoms for two and one-half years and does heavy work.

Fig. 2.—Infra-red photograph of the anterior wall of the chest. There is a marked increase of the venous collateral network on the affected (right) side.

This case was interpreted as one of traumatic axillary thrombosis which set up a vasomotor reflex, which was responsible for the flushing and the pain and even for part of the edema. Since the edema disappeared after the afferent arc of the reflex was interrupted, it was not due, or not entirely due, to the venous obstruction.

CASE 5.—B. H., a 38 year old laborer, was first seen in the neurocirculatory disease clinic of the University of Illinois College of Medicine on Nov. 19, 1935, complaining of pain and stiffness of the left foot and ankle. He was quite well until last June, at which time he opened a small abscess below the left external malleolus. In a few days the foot became swollen and painful, and the patient had to stay in bed with a severe infection. The original opening drained little, but the swelling involved the whole foot and ankle. In July a cast was put on, but the leg became so painful that the patient cut the cast off in forty-eight hours. Another loose cast was applied and left on for a week or ten days. Since then the patient has been up and around, limping and hobbling on crutches. The ankle was stiff, and weight bearing was painful.

The physical examination revealed nothing of note, with the exception of the affected extremity and chronic bronchitis. The left lower extremity was definitely atrophic compared with the right (fig. 4). The measurements of the thighs and calves revealed a difference of 1½ inches (3.8 cm.) in circumference of the thigh and 1¼ inches (3.2 cm.) at the midcalf.

The musculature of the calf was definitely shrunken compared with the normal side but seemed in a state of hypertonus. The skin was cold, and there was a cyanotic discoloration of the entire foot, especially in the depending position. The pulsations of the arteries seemed normal. The motion in the ankle joint was limited to 5 degrees. There was a marked valgus position of the ankle.

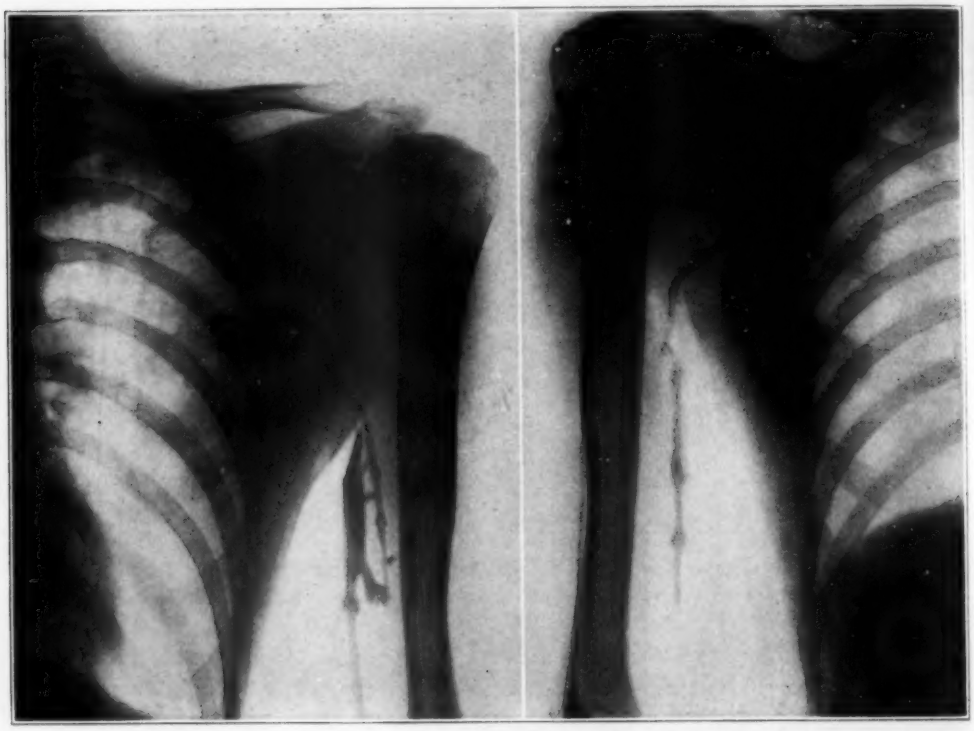

Fig. 3.—Visualization of the axillary and subclavian veins by the injection of skiodan into the cubital vein. The block in the subpectoral portion of the subclavian vein has been accentuated by retouching the print. It was very definite in the film. There is a marked filling of the cephalic vein which serves as the main collateral. This was absent on the left side, used for control. The subpectoral portion of the subclavian vein is quite distinct.

Below the outer malleolus a small pigmented scar was seen, which was freely movable and not attached to the bone. This was the site of the original infection. Pain was felt on dorsiflexion and on putting weight on the leg. Cutaneous sensation and the reflexes were normal. Paresthesia involving the whole foot was present. There was no element of compensation in this case.

Oscillometric curves taken before the operation revealed an increased inflow of blood into the lower extremities; in the left leg oscillations started at 280 mm. of mercury, and the diastolic pressure was read at 105 mm.; on the normal leg the oscillations were seen even at 300 mm., and the diastolic pressure was read at 75 mm. The lower systolic pressure here could readily be explained by the smaller size of the limb, whereas the definitely higher peripheral resistance might have been due to increased spasm or an organic obstruction. As the pedal pulses were well palpable, the latter possibility is not likely.

After the administration of 100 mg. of procaine hydrochloride intraspinally, resulting in anesthesia to the level of the navel, the blood pressure in the left lower extremity fell to 140 systolic and 85 diastolic and in the right lower extremity to 140 systolic and 80 diastolic, making them practically equal. This fall in pressure and the striking diminution of the stroke volume were not accompanied by a fall in blood pressure in the arm, which stayed at 115 systolic and 75 diastolic during the entire period of anesthesia. A week after left lumbar sympathectomy was performed the pulse waves of the lower extremities seemed fairly identical; the left was 160 systolic and 81 diastolic, and the right, 155 systolic and 85 diastolic, with slightly higher waves on the right side. This is readily explained by the difference in the size of the limb.

Fig. 4.—Marked atrophy of the left leg and thigh following a low grade chronic infection of the subcutaneous tissue at the external malleolus. The picture has been reversed.

Roentgen examination of the ankles and the lower part of the legs revealed marked atrophy of the spongiosa and cortical shells of the tarsal and metatarsal bones, of the calcaneus and the femur, of the tibia and the fibula (fig. 6).

The patient was followed in the dispensary after the operation. Four weeks later he was stepping on the affected leg quite freely. He still had a partial

ankylosis of the ankle, which because of lack of adequate physical therapy had not had active and passive exercise. He was instructed to apply heat and to massage the ankle at home.

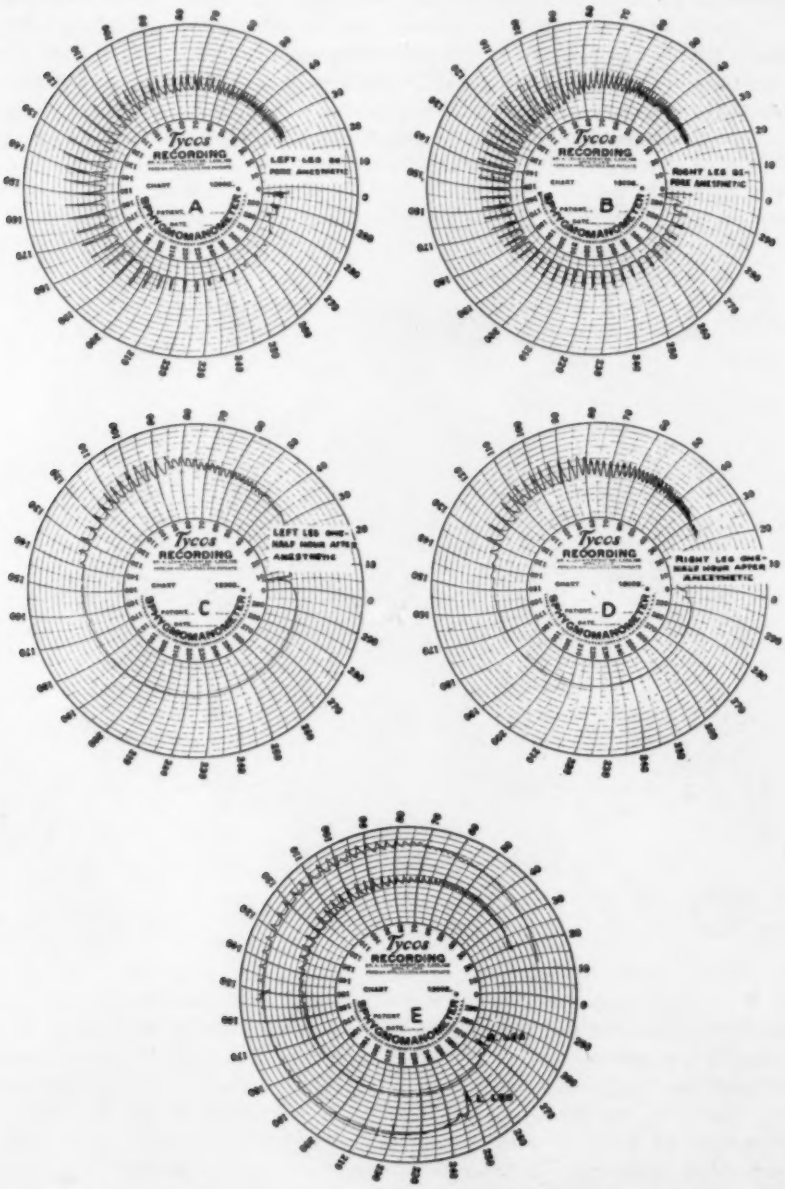

Fig. 5.—Oscillometric curves in case 5 illustrating the marked increase in inflow into the lower extremities (*A* and *B*) which was abolished after spinal anesthesia (*C* and *D*) and after lumbar sympathectomy (*E*). In *E* the lower curve was made from the affected left leg after lumbar sympathectomy and the upper curve from the normal extremity.

Six weeks after the operation walking was painless. The crutch was abandoned. There was still a limitation in dorsiflexion, but plantar flexion was free. The patient had not used the leg much because of the unusually heavy snowfall. Three months after the operation the saturation of venous oxygen, which rose immediately after sympathectomy, was maintained. The vasomotor disturbances had disappeared. The ankylotic ankle joint and the valgus position of the ankle still caused trouble. Because of external circumstances, the patient was unable to obtain any kind of physical therapy, but a few active and passive exercises were prescribed, together with an adequate arch support.

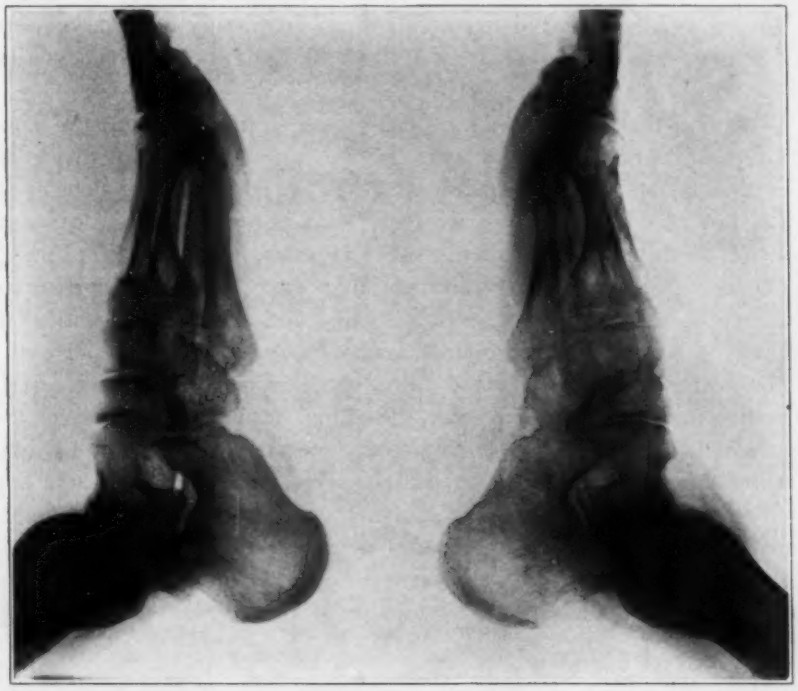

Fig. 6.—Atrophy of the spongiosa and cortical shells of the calcaneus and the tarsal and metatarsal bones. The control film is on the left.

COMMENT

In the five cases presented the initial stimulus for the vasomotor and trophic changes included a single mild trauma (case 1), massive venous thrombosis (case 4), pelvic periphlebitis (case 2), nodular phlebitis (case 3) and a neglected infection (case 5). The common factor in all these cases was the rather mild and insignificant injury to the tissue which caused the widespread trophic disturbance in the affected limb. It is obvious that a large number of such injuries, infections or thromboses occur day after day without producing such consequences. Why, then, one must ask, will this syndrome appear in certain, seemingly rare cases?

To answer this question one must first inquire how rare or how frequent this "reflex dystrophy" really is. Since my attention has been focused on this syndrome, I have found it in a great many cases of venous thrombosis, blunt trauma, lymphatic block or low grade infection. These vasomotor and trophic changes, however, are slight and gradually subside. I have also repeatedly seen a marked hard edema accompanying Buerger's disease disappear immediately after sympathectomy, thus demonstrating that it is not always due to venous block. One must say then that although in its full, intractable form the disease is infrequent, mild, masked abortive forms can frequently be observed, but they will spontaneously subside with the healing of the original exciting cause.

What is it that makes this peculiar disease so intractable that a number of patients requested and were granted amputation? In my small series the patient in case 1 definitely had borderline mental deficiency, with a low intelligence quotient; there was also the element of compensation in this case. In all my other patients, with the exception of the one in case 4, a physically and mentally normal, husky young man, an imbalance of the vegetative nervous system and a neurotic constitution could easily be detected. A neurotic constitution is obviously not easily defined and is so often referred to as constitutional inferiority. It is interesting to note, however, that the spinal mechanism, whereby the preganglionic neurons of the sympathetic nervous system can be activated by somatic nociceptive stimuli, is not as active if the medulla and the higher centers retain their normal connections with the spinal sympathetic outflow. The application of the work of Brooks [12] to this problem means that if the inhibition of higher centers is lacking or diminished, this spinal somatic-sympathetic reflex may become exaggerated or fixed.

Acute reflexes, especially those originating from diseased or thrombosed veins and arteries, are well known, and I have recently commented on the important reflex vasospasm which accompanies sudden arterial occlusions and which may often—and not the original plug itself—be the cause of gangrene.[13] As long as the peripheral blood vessels lack any other but somatic afferent nerves,[14] the afferent arc must follow the ordinary sensory pathways and enter the posterior horn through the posterior root ganglion. Because lumbar sympathectomy

12. Brooks, C. M.: Reflex Activation of the Sympathetic Nervous System in the Spinal Cat, Am. J. Physiol. **106**:251, 1935.

13. de Takáts, G.: Acute Arterial Occlusions of the Extremities, Am. J. Surg. **33**:60, 1936.

14. Moore, R. M., and Singleton, A. O., Jr.: Studies on the Pain Sensitivity of Arteries: II. Peripheral Paths of Afferent Neurons from the Arteries of the Extremities and of the Abdominal Viscera, Am. J. Physiol. **104**:267, 1933.

abolishes the danger of gangrene from high arterial ligature,[15] the efferent arc of this reflex must go through the sympathetic efferent nerves which leave the cord from the lateral horn through the anterior roots, join the peripheral mixed nerves and are given off to the vessels in segments. Such an acute reflex vasospasm may last—if untreated—for from twenty-four to forty-eight hours and is due to a sudden powerful stimulation of sensory nerves, especially—it would seem—around blood vessels.

In these cases of reflex dystrophy, however, a slow, continuous afferent impulse is being dealt with which may have vasoconstrictor (pressor) or vasodilator (depressor) effects. It is a long known fact of physiology that strong stimulation of the central end of an afferent nerve elicits pressor effects, whereas weak stimuli or stronger stimuli in a regenerating nerve produce depressor effects. The local depressor effects of stimulation of sensory nerves have been described by Lovén and are usually named after him. These effects have been studied by Bayliss [16] (fig. 7). Lovén found that stimulation of the divided central end of a sensory nerve in the rabbit's ear caused marked vasodilatation in the ear, which in turn could be prevented by cutting the cervical portion of the sympathetic trunk. He also found that when a peripheral nerve in the hindleg was stimulated, the volume of the limb increased. Bayliss felt that dilatation of the vessels causing the increase in the size of the limb was due both to excitation of dilator fibers and to inhibition of constrictor fibers. He assumed that all dilator fibers were in the posterior root and that the abdominal sympathetic nerves carried only constrictor fibers (fig. 8), a thesis which has received modification since his time.[17]

The difference in the vasomotor responses elicited by weak and strong stimulation of afferent nerves can be explained, according to Ranson and Billingsley,[18] by the variations in the resistance to afferent conduction offered by different central pathways. According to their findings, weak impulses reaching the spinal cord are conveyed upward in the depressor path, in the ventral parts of the lateral funiculi containing long fibers with few relays, whereas the pressor impulses are con-

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15. Mulvihill, D. H., and Harvey, S. L.: Studies on Collateral Circulation: Thermal Changes After Arterial Ligation and Ganglionectomy, J. Clin. Investigation **10**:423, 1931.

16. Bayliss, W. M.: The Vasomotor System, London, Longmans, Green & Company, 1923.

17. Lewis, Thomas, and Pickering, G. W.: Vasodilation in the Limbs in Response to Warming the Body, with Evidence for Sympathetic Vasodilator Nerves in Man, Heart **16**:33, 1931.

18. Ranson, S. W., and Billingsley, P. R.: Vasomotor Reactions from Stimulations of the Floor of the Fourth Ventricle, Am. J. Physiol. **41**:85, 1916.

ducted upward at the apexes of the dorsal gray columns through paths composed of short fibers with frequent relays.

To apply these studies to the present problem, the possibility of different reflex paths must be considered. Andrews published the report of an interesting case of edema following radical amputation of the breast in which section of the posterior roots was done for the intractable pain.[19] The edema promptly disappeared and only reoccurred after a week. In his diagram the vasomotor reflex arc is led through the sympathetic chain to the posterior root ganglion and from there into the posterior horn; the efferent arc is through the anterior roots, joining the vessels through the sympathetic nerves. Since the findings of Moore and Singleton,[14] who could elicit a painful response from a peripheral vessel after lumbar sympathectomy, it seemed likely that sensation from the arteries of the extremities is mediated by the spinal nerves. And

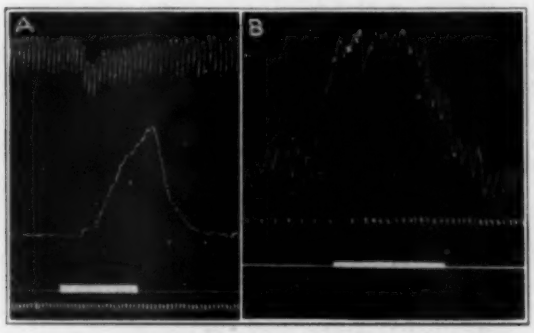

Fig. 7.—Curves showing the Lovén reflexes. In *A*, the upper curve represents the blood pressure; the lower curve, the volume of the upper part of the hindlimb of a dog. At the mark of signal the central end of the dorsalis pedis nerve of the same leg was stimulated, causing marked dilatation of the leg with a slight fall in blood pressure. The usual rise of general pressure was absent here. In *B*, the upper curve represents the blood pressure; the lower curve, drops of blood falling from the cut femoral vein. At the mark of signal the central end of the anterior crural nerve was stimulated. A rise of blood pressure is seen, accompanied by vasodilatation in the leg. (From Bayliss, W. M.: The Vasomotor System, Longmans, Green & Company, London, 1923.)

yet the fact remains that certain painful syndromes in the extremities, such as causalgia, stump neuralgia and meralgia paraesthetica, are favorably influenced by blocking the sympathetic nervous system with procaine hydrochloride or by sympathectomy. In accordance with a diagram which I published to explain the acute reflex vasospasm following arterial occlusion, sympathectomy may act by interrupting the efferent arc, thus abolishing the reflex vasomotor, pilomotor and sweat-

19. Andrews, E.: The Vasomotor Reflex Arc, Ann. Surg. **85**:116 (Jan.) 1927.

ing phenomena (fig. 9). In cases 2, 3 and 5 there was evidence that such a reflex was successfully interrupted by sympathectomy. In cases 1 and 4, however, the focus of irritation on the afferent side was eliminated, resulting in equally good results. One cannot discuss, however, such nutritional reflexes without considering the vasodilator fibers in the posterior roots. Some evidence has recently been accumulating that there are vasodilator efferent fibers in the dorsal roots with cells of origin in the dorsal root ganglions, accessible to reflex activation via synapses within the cord.[20] The literature on the production of vasodilatation by stimulation of the posterior roots has been summarized by Kahr and Sheehan.[21] But so long as such fibers can be sectioned only by sacri-

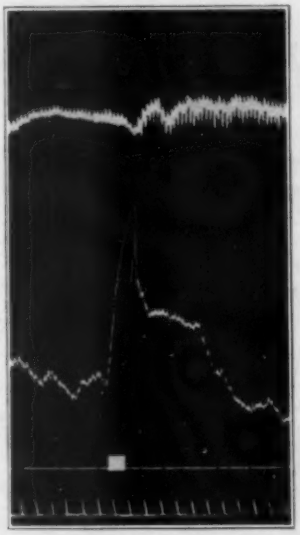

Fig. 8.—Excitation of posterior root vasodilators in the Lovén reflex. The upper curve indicates the blood pressure; the lower curve, the volume of the hindlimb of a dog. The abdominal sympathetic nerves were extirpated and the viscera removed. At the mark of signal, the central end of the anterior crural nerve of same leg was stimulated. (From Bayliss, W. M.: J. Physiol. **28**:276, 1902.)

ficing the sensation of the extremity, their interruption is not practicable except in cases of intractable pain. When disease destroys the posterior roots, as in tabes, syringomyelia and spina bifida, trophic ulceration occurs. Treatment by sympathectomy has been entirely unsuccessful in my hands. The reasons for this are the absence of axon reflexes and

20. Bishop, G. H.; Heinbecker, P., and O'Leary, J. C.: The Function of the Nonmyelinated Fibers of the Dorsal Roots, Am. J. Physiol. **106**:647, 1933.

21. Kahr, S., and Sheehan, D.: The Presence of Efferent Fibers in Dorsal Roots, Brain **56**:265, 1933.

possibly the lack of any spinal reflexes activated by somatic impulses.

The oscillometric studies in case 5 have revealed the interesting fact that in the affected dystrophic extremity as in its fellow a continuous depressor reflex (Lovén reflex) was operating which was equally abolished by spinal anesthesia (afferent arc) and by lumbar sympathectomy (efferent arc). The spinal anesthesia might, of course, have affected the sympathetic efferent nerves, although it did not reach high enough to abolish sweating above the knee. In case 2 there was definite vasoconstriction, which occurs, according to Sudeck [18] and Fontaine and Herrmann,[7] in the later stages.

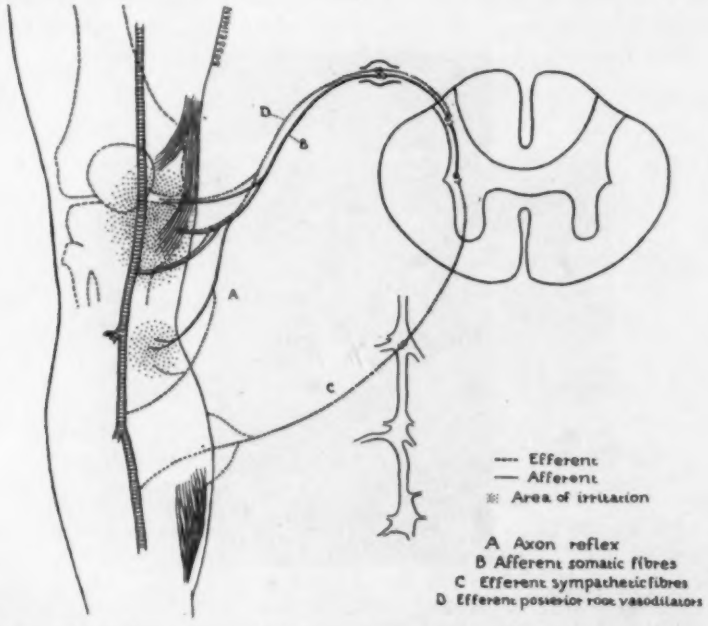

Fig. 9.—Vasomotor and nutritional reflexes originating in the tissues. Clinical experience would indicate that such stimuli are especially apt to originate around blood vessels and joints and tendons.

Gask and Ross [22] gave a different explanation for the beneficial effect of sympathectomy in a case of causalgia associated with herpetic vesicles. They expressed the belief that the increased flow of blood after sympathectomy insures the rapid removal of tissue products, including the H substance which dilates vessels and forms herpetic vesicles. Following the work of Sir Thomas Lewis, they explained the vasomotor phenomena of causalgia on the basis of an antidromic impulse originating from an irritated sensory nerve. While this mecha-

22. Gask, G. E., and Ross, J. P.: The Surgery of the Sympathetic Nervous System, Baltimore, William Wood & Company, 1934.

nism may be operating in certain types of causalgia, my cases show that small foci of irritation may maintain a widespread vasomotor and trophic disturbance which can be relieved by interrupting either the afferent or the efferent arc of the reflex. While many authors, starting with Sudeck, have spoken of a reflex trophoneurosis, the pathway of such a reflex has not been examined in detail.

CONCLUSIONS

The most likely pathway, then, for this peculiar nutritional reflex, which must be differentiated from the short axon reflexes or from vasodilator responses to stimulation of the efferent nerves in partial injury to the nerves, is a chronic focus of irritation in the periphery, a weak, continuous impulse through ordinary sensory pathways to the cord and a relay, following the pathway of least resistance to the lateral horn, and from here a sympathetic efferent impulse to the tissues. That this reflex is more active when higher centers are not inhibited has been shown experimentally, and this may explain why reflex dystrophy occurs more readily in mentally unstable or defective persons. It is obviously not easy to differentiate it in its early forms from malingering, anxiety neurosis or hysteria. A temporary block of the sympathetic outflow is of great diagnostic aid. The spotty atrophy of the bone, which occurs very early, is another important sign. At a later stage the atrophy of the skin, nails and muscles becomes evident; the atrophy of the bone is now diffuse and cannot be differentiated from atrophy due to inactivity. That low grade infection in the bones, joints and tendons should be carefully excluded is obvious.

The excision of the irritable focus was possible in three of my cases; should this be impossible, the efferent arc of the reflex can be interrupted by sympathectomy, which seemed equally effective. This operation has been recently advocated by Brauecker [4c] and Rieder [23] for such conditions. Reflex dystrophy has been unrecognized for many years and should be particularly understood by men engaged in estimating disability after injuries. It occurs frequently but usually subsides under mild, not overzealous physical therapy. Heat, immobilization and diathermy have been successful in many of the cases of milder involvement; the patients for whom I advised sympathectomy had already been found resistant to conservative therapy before the afferent or efferent arc of the reflex was interrupted. These cases also show that outside of fractures, injuries and infections of the soft tissues, venous thromboses and periphlebitis are also capable of activating this reflex.

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23. Rieder, W.: Operative Behandlung der akuten schweren Extremitätendystrophie, Arch. f. klin. Chir. **180**:368, 1934.

SUMMARY

Five cases of reflex dystrophy of the extremities have been described. One followed a mild injury to the soft tissue, one a pelvic lymphangitis, one an axillary thrombosis, one a nodular phlebitis of the veins and one a low grade infection of the soft tissues. In all of these cases the local alteration of tissues maintained an exaggerated nutritional reflex, leading to vasomotor and trophic phenomena. The possible pathways of this reflex were discussed, together with methods of treatment.

NOTE.—Since this article was submitted for publication, four additional cases have been observed; in one the condition followed a mild injury to the foot; in one, lymphangitis of the toe; in one, an injury to the wrist by strapping on the operating table, and in one, an injury to the middle finger. In the last case, in addition to an increased blood flow, there were marked herpetiform eruptions. In two of the cases sympathectomy had been performed, with cessation of symptoms. All four cases support the observations made in the article.

SIXTY-SECOND REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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CONGENITAL DEFORMITIES

Congenital Dislocation of the Hip.—Bauer [1] condemns the treatment of congenital dislocation of the hip by a plaster cast, maintaining that there is no growth in the joints during such fixation. Even if immediately after such treatment the function seems good, arthritis or subluxation occurs later. He is of the opinion that early recognition of the condition can be made, i. e., in the fourth to the eighth week, by observing the posture of the infant. At this age replacement is secured without an anesthetic, and the position is maintained by the application of a webbing brace so arranged that the knees are drawn apart by attaching them to a band around the lower part of the thorax. Natural mobility is unhindered, only adduction and extension of the hip being prevented, and very good musculature develops, especially around the hip. The result of the treatment in all cases is a rapid mechanical cure without danger of recurrence, owing to the natural development of the joint and its soft parts. Twenty-seven children have been treated by

This report of progress is compiled from a review of 148 papers selected from 306 titles relating to orthopedic surgery, which appeared in the medical literature approximately between July 1, 1936, and Nov. 1, 1936. Only those which suggested progress were chosen for review.

1. Bauer, F.: Congenital Dislocation of Hip, Lancet **1**:1057-1059, 1936.

this method, 21 of whom were in the first year of life and the remaining 6 of whom were in the second year.

The Acetabular Index in Infants in Relation to Congenital Dislocation of the Hip.—In a study of normal and of congenitally dislocated hips Kleinberg and Lieberman [2] draw attention to the angle of inclination of the roof of the acetabulum as an index of dislocation or subluxation. They coin the term acetabular index and define it as the angle formed between the roof or iliac portion of the acetabulum and a horizontal line passing through the triradiate cartilages. They found this index to average 27.5 degrees in normal infants. In infants of 2 years the normal angle averaged 20 degrees. In those with congenital dislocation of the hip the average index was 37.5 degrees. If the index is 30 degrees or more in an infant, they suggest that the hip is in danger of slipping out and should be treated in abduction, as advocated by Putti.

[ED. NOTE.—Efficacy in the treatment of congenital dislocation of the hip seems to depend chiefly on early diagnosis and early fixation with the thighs in abduction. Later therapy must usually consist of extensive operative procedures, with no definite assurance of success.]

Treatment of Pes Adductus.—Dengler [3] discusses the treatment of pes adductus from a review of 32 cases. Two thirds of the patients were males, and in 23 the deformity was bilateral. There were metatarsus varus and deformity of the tarsal bones on the medial side of the foot in most cases. In 17 patients (young patients with mild deformity) manual manipulation and the use of plaster casts sufficed. In 2 cases it was necessary to perform manipulation under anesthesia. Seven patients were operated on after the manner of Camera, the fascia and joint capsule at the scaphoid-cuneiform and first metatarsal joints being stripped. In the remaining 6 cases (older patients, from 5 to 11 years), a wedge-shaped osteotomy of the cuboid bone was necessary in addition to the operation of Camera.

Congenital Flexion and Ulnar Deviation of the Fingers (Deviation in Coup de Vent).—Dreyfuss [4] reports 4 cases of congenital deformity of the fingers in flexion and ulnar deviation. He believes that the chief factor in their causation was a contraction in the volar accessory ligament. In no case was any bony abnormality observed. Other associated

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2. Kleinberg, S., and Lieberman, H. S.: The Acetabular Index in Infants in Relation to Congenital Dislocation of the Hip, Arch. Surg. **32**:1049-1054 (June) 1936.

3. Dengler: Zur Klinik Therapie der Pedes adducti, Ztschr. f. Orthop. **65**: 121-129, 1936.

4. Dreyfuss, M.: Beitrag zum Bilde der angeborenen "Windmühlenflügelstellung" der Finger (Déviation des doigts en coup de vent), Ztschr. f. Orthop. **65**:205-225, 1936.

deformities, such as clubfoot, were not uncommon. Operative correction was attempted in 2 cases. A tourniquet was used; an incision was made between the fingers, and the joint capsule and aponeurosis were incised on the lateral side of the finger. The accessory volar ligament was freed at its distal end. The superficial fibers of the adductor pollicis and opponens pollicis muscles were cut, permitting the thumb to be brought into abduction. The hand was placed on a splint in the corrected position. The author reports almost complete correction of the deformity and good function after operation.

[ED. NOTE.—One of the editors has observed marked improvement in 2 cases after daily passive stretching with a corrective hand cast worn at night.]

Scoliosis in Infants.—Harrenstein [5] reports 46 cases of scoliosis in infants under 2 years of age. None of these showed any congenital abnormalities. All had rotation deformity of the ribs, and none had rickets. The girls outnumbered the boys 29 to 17. In 37 of the 46 infants a single curve was present, it being to the left in 29; in the remaining 9 double scoliosis was present. The cause of these curves was unknown. Treatment consisted of complete recumbency in corrective plaster shells. The treatment was kept up for as long as two years if necessary. When the patient was first allowed up, a supporting corset was worn. In 50 per cent of the cases the condition was considered cured at the end of a follow-up period of from one to six years.

SYPHILIS

Congenital Syphilis of the Bone.—By a study of roentgenograms, Jung [6] was able to diagnose congenital syphilis when the serologic test was negative. He quotes the figures given by McLenvey and Turner. Of 54 infants born of syphilitic mothers, with a positive Wassermann reaction of the cord blood, 81.4 per cent were ultimately found to be syphilitic. Of 283 infants also born of syphilitic mothers but with a negative Wassermann reaction of the cord blood, only 13.7 per cent were found to have congenital syphilis. It may be said that negative roentgenographic findings are not conclusive, but that positive roentgenographic findings offer one of the most conclusive and one of the earliest diagnostic signs of congenital syphilis. Jung analyzes the roentgenographic findings in 62 cases of syphilis in infants under 1 year of age. He discusses osteochondritis, which is described as an increase in the width of the provisional zone of calcification of the long bones, which is shown roentgenographically as a dense cap at the diaphysial end.

5. Harrenstein, R. J.: Sur la scoliose des nourrissons et des jeunes enfants, Rev. d'orthop. **23**:289-307, 1936.

6. Jung, T. S.: Congenital Bone Syphilis, Chinese M. J. **50**:352-363, 1936.

When this lesion is farther advanced it should be considered as an osteomyelitic change. Actual osseous destruction may be seen, and there may occur an infraction of the zone of provisional calcification. Osteomyelitis is the most common lesion in advanced osteochondritis and is most frequently characterized by punched-out symmetrical rarefactions which are seen in the upper and inner aspects of the tibia. Periostitis is discussed in detail. It is seldom found as the sole lesion of congenital syphilis in early infancy but usually accompanies advanced osteochondritis. Excellent roentgenograms are shown.

OSTEOMYELITIS

Dengler[7] reports 38 cases of osteomyelitis. In 23 of these cases the patients were treated by Orr's method of drainage, petrolatum packs and undisturbed rest in a cast. The remaining 15 were treated by Löhr's modification (extreme drainage, resection into normal bone, cod liver oil packs, interrupted suture of the skin, the application of a cast and rest). In 23 of the 38 cases the lesions completely healed. At the time of the report it was more than nine months since operation in all the cases. The details are not given. Eight of the patients had tiny fistulas, and in 7 small sequestrums had been picked out. Both methods of treatment seemed about equally effective.

Pusitz and his co-workers[8] review the literature on osteomyelitis of the spine and report 6 additional cases. They point out numerous errors that are commonly made in diagnosis. Certain general principles in therapy are given: Drainage of the osteomyelitis should usually be delayed until the diagnosis and the area involved are known. The patient should be kept on a Bradford frame with head and pelvic traction if there is much pain on motion. Transfusion of blood is the most effective supportive measure. The Orr treatment for vertebral lesions is advocated. Fusion of the involved area of the spine may be necessary later. Dependent drainage of abscesses should be carried out when possible. Where there are signs of compression of the spinal cord, laminectomy usually brings prompt relief.

Disturbance of Growth Following Osteomyelitis.—Wilson and McKeever[9] studied 57 patients with 85 individual foci of osteomyelitis. Sixty-two per cent of the bones showed some sort of a disturbance of growth on clinical examination. Hypertrophy of the diameter of the

7. Dengler: Zur Behandlung der chronischen Osteomyelitis nach Orr und Löhr, Arch. f. klin. Chir. **186**:1-15, 1936.

8. Pusitz, M. E.; Owen, A. K.; Finney, G. A.; Lattimore, J. L., and Gerundo, M.: Osteomyelitis of Spine, J. Kansas M. Soc. **37**:265-287 and 313-324, 1936.

9. Wilson, J. C., and McKeever, F. M.: Bone Growth Disturbance Following Hematogenous Acute Osteomyelitis, J. A. M. A. **107**:1188-1193 (Oct. 10) 1936.

shaft of the bone was always present. Lengthening of the bone occurred in 21 per cent of the bones. The infections that resulted in lengthening were always situated in the diaphysis and left the epiphysial line undamaged. The same percentage of bones showed shortening, and this was the result of changes in the epiphysial line due to adjacent infection. Other deformities found were disturbance of the inclination of the joint in the hips, knee and ankle and a diminution in the size of the foot after infection higher up in the leg and thigh.

TUBERCULOSIS

A Survey of Tuberculosis of the Bones and Joints in Detroit's Municipal Sanatoriums.—Birkelo and Jarzynka[10] present data to show that there is a marked decline in the incidence of tuberculosis of the bone. In 1929 there were 70 patients with osseous tuberculosis in the municipal sanatoriums of Detroit, which represented 6 per cent of all hospitalized patients with tuberculosis, while in 1933 and 1934 there were only 22 and 16, respectively, which represents 2 and 1.5 per cent for each of these years. This marked decrease is explained by the fact that osseous tuberculosis is usually secondary to a primary focus elsewhere, that this primary focus is being recognized earlier and that treatment is instituted sooner, thus preventing secondary complications. According to the authors, on the basis of population there was a higher percentage of Negroes with pulmonary tuberculosis in the city hospitals than of white persons and an even higher percentage of Negroes with osseous tuberculosis. Twenty-five per cent of the entire series of patients with osseous tuberculosis were Negroes. The location of the lesions in their respective order of frequency was as follows: spine, hips, knee, ribs, ankles, fingers, elbows, toes, wrists, sternum, shoulders, pelvis, clavicles, jaws and skull. Roentgenograms and a discussion of signs which lead to early diagnosis are included in the report.

Frozen Section Diagnosis of Tuberculous Joints.—Swift,[11] from a study of 175 patients suspected of having tuberculosis of the joints, arrived at certain conclusions as to the value of methods of diagnosing this condition, i. e., frozen section at the time of operation, paraffin section and inoculation of guinea-pigs. He found that frozen sections were not satisfactory in 18 per cent of cases and that paraffin sections showed tuberculosis in 23 of the 175 cases in which the diagnosis was not proved by frozen sections. Inoculation of guinea-pigs was done in 133 cases, and the diagnosis was proved 113 times. Swift emphasizes

10. Birkelo, C. C., and Jarzynka, F. J.: Survey of Bone and Joint Tuberculosis in Detroit Municipal Sanatoria, Am. J. Roentgenol. **36**:44-51, 1936.

11. Swift, W. E.: Frozen-Section Diagnosis of Tuberculosis Joints, J. Bone & Joint Surg. **18**:641-647, 1936.

(1) that satisfactory tissue must be taken for section; (2) that careful preparation of the frozen section is necessary and (3) that a careful inspection of the slides must be made.

[ED. NOTE.—In spite of the accuracy of diagnosis gained from tissue section and inoculation of guinea-pigs, in the vast majority of cases it is seen from Swift's figures and is known from experience that the clinical and roentgenographic aspects of the case must be considered. The experience and judgment of the surgeon at the time of operation is of the utmost importance in making the decision as to the question of fusion of the joint. In cases in which tuberculosis of the joint is suspected biopsy may not be necessary for diagnosis if the patient is observed for some time and if aspiration is used as a diagnostic method.]

Tuberculosis of the Hip in Children.—Barr [12] studied 106 consecutive patients with tuberculosis of the hip at the New England Peabody Home for Crippled Children. In 15 per cent it was later learned that an incorrect diagnosis had been made. Fifteen of the patients died—7 of tuberculous meningitis, 6 of secondary infection and amyloid disease and 2 of pulmonary tuberculosis. The disease was found to run a variable course, and cure was never certain, but the condition was frequently arrested. Arrest of the disease with a useful range of motion occurred too rarely to make it an expected result in the case in which conservative treatment is used. After long-continued conservative therapy to arrest the disease, operative fusion of the hip joint offered the best chance of a stable, weight-bearing limb.

Abscess of Firmly Ankylosed Tuberculous Hips.—Adams [13] observed the development of a tuberculous abscess in 6 of 30 patients with tuberculosis of the hip on whom an operation has been performed previously. The abscesses developed after ankylosis of the hip occurred.

[ED. NOTE.—These papers show that one can never be certain of cure in cases of osseous tuberculosis. The disease may progress in a joint in which bony ankylosis has occurred.]

CHRONIC ARTHRITIS AND BURSITIS

Spondylitis Deformans of the Cervical Portion of the Spine.—From a study of roentgenograms of the cervical portion of the spine for 140 persons of varying ages admitted to the hospital for various reasons, Ober [14] found positive evidence of spondylitis deformans in 57 per cent

12. Barr, J. S.: Tuberculosis of the Hip in Children, J. A. M. A. **107**:1517-1522 (Nov. 7) 1936.

13. Adams, Z. B.: The Occurrence of Abscesses from Tuberculous Hips That Are Firmly Ankylosed, J. Bone & Joint Surg. **18**:974-978, 1936.

14. Ober, G.: Ueber "Spondylitis deformans" der Halswirbelsäule, Deutsche Ztschr. f. Chir. **246**:666-684, 1936.

of those between the ages of 35 and 40 and in 85.7 per cent in the age group of 60 or above. No relationship was found between the extent of the roentgenographic change and the clinical symptom of pain. In 15.8 per cent of those with roentgenographic changes and in 6.5 per cent of those without roentgenographic changes subjective disturbances were recorded. The prodromal state of the lesion might make itself roentgenographically apparent with isolated calcification of the anterior ligaments, osteophytic formations at the point of attachment of the anterior ligaments or by deformity of individual vertebral bodies.

Arthritis and Injuries to Joints.—Kling [15] calls attention to the value of examination of effusion from the joints both from a diagnostic and from a therapeutic point of view. He believes that there are definite diagnostic differences between traumatic and inflammatory effusion. If there has been recent trauma, the effusion may be hemorrhagic and contains a mucinous body, which he considers to be a secretory product. Fat globules may be present if the injury is severe. Centrifugation easily demonstrates their presence. Cytologic examination may reveal bone marrow cells in addition to the usual blood constituents. Kling points out that if the icteric index of the fluid is 5 or more, the effusion is traumatic or more rarely due to hemophilia, xanthoma, sarcoma or tabetic arthropathy. An inflammatory effusion has an index of less than 5. Fluid from hypertrophic arthritic joints shows a high viscosity with a small number of cells, chiefly monocytes and synovial lining cells. In villous arthritis over 15 per cent of the cells are synovial.

Transient Synovitis of the Hip Joint.—Finder [16] reviews the histories of 22 children with transitory synovitis of the hip joint. The average age in his series was 5.4 years, the youngest patient being 11 months and the oldest, 14 years. The chief symptoms of this condition are pain, limp and muscular spasm. The temperature and white blood cell count may be elevated slightly. The tuberculin test and roentgenographic examination usually give negative results. The differential diagnosis includes tuberculosis, and a period of rest in bed under observation may aid one in making the diagnosis. The acute phase generally lasts from two to four weeks, and the treatment consists of rest in bed and traction or immobilization in a plaster spica. All the patients in Finders' series recovered completely.

Treatment of Subacromial Bursitis by Roentgen Therapy.—Lattman [17] believes that roentgen therapy gives quicker relief from pain and

15. Kling, D. H.: Arthritis and Injuries to Joints, Arch. Surg. **33**:213-224 (Aug.) 1936.

16. Finder, Jerome G.: Transitory Synovitis of the Hip Joint in Childhood, J. A. M. A. **107**:3-5 (July 4) 1936.

17. Lattman, I.: Treatment of Subacromial Bursitis by Roentgen Irradiation, Am. J. Roentgenol. **36**:55-60, 1936.

an earlier restoration of function than any other method of treatment for subacromial bursitis. The usual dosage is about 350 roentgens. Twenty patients were treated; a brief history and the result of a follow-up study of from one to five years are given in tabular form regarding each patient. One treatment was usually sufficient. The immediate effect of the roentgen therapy was usually increased pain for about twenty-four hours, which was controlled with a sedative. After this there was rapid abatement of symptoms, with complete relief in many cases in one week. A calcified deposit was observed in 5 cases; in 3 the deposit disappeared completely in two months.

Treatment of Tennis Elbow.—Cyriax [18] believes that the usual pathologic picture in tennis elbow is a tear at the periosteal attachment of the extensor carpi radialis brevis muscle to the lateral epicondyle. His method of treatment, which was successful in all but 1 of the 22 cases reported, consists of deep massage over the painful region with the elbow flexed at 90 degrees. This is followed by passive extension of the forearm to 180 degrees and forced adduction of the forearm on the arm. Anesthesia is not required, and the procedure is repeated at intervals of two or three days for four or five treatments. It may be used in recent or in old cases. The literature on tennis elbow is reviewed fully.

NEOPLASMS

Tumors of the Bone.—The second edition of the valuable work of Geschickter and Copeland [19] contains the added result of a study of a large number of osseous neoplasms. The introductory portions on the interpretation of clinical findings by Dean Lewis and on diagnostic and therapeutic procedures by the late Joseph Bloodgood should be particularly helpful. The tumors of bone are grouped according to their derivation from embryonic or postembryonic types of tissue. The book is written in a clear manner and is well illustrated with reproductions of roentgenograms and photomicrographs. A well selected bibliography is added to each chapter.

Roentgenographic Stages in the Growth of Osseous Cysts.—Why do some simple osseous cysts yield readily to surgical intervention and others not? Févre [20] believes that the answer lies in the fact that some of the cysts are in an active growing stage and others in a quiescent,

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18. Cyriax, J. H.: The Pathology and Treatment of Tennis Elbow, J. Bone & Joint Surg. **18**:920-940, 1936.

19. Geschickter, C. F., and Copeland, M. M.: Tumors of the Bone, New York, American Journal of Cancer, 1936.

20. Févre, M.: Les étapes radiologiques dans l'évolution du kyste des os, Rev. d'orthop. **23**:131-142, 1936.

stable state. He divides simple, benign cysts into three types. The first type is the growing cyst. This cyst is characterized by the total lack of any definite limit (in roentgenogram) at its diaphysial border. No line can be drawn between the margin of the cyst and the medullary canal. The cyst does not respond well to operation and is prone to recur. The second type is the stable or quiescent cyst. This cyst shows a definite lower limit consisting of a dense layer or shell of bone separating the cyst from the medulla. The cyst responds well to operation and does not tend to recur. The third type is the stable but enlarging cyst. This cyst is also stable, and while it does not tend to progress down the shaft of the bone, it enlarges in diameter. The cyst also responds favorably to operation. The author believes that these types of cysts represent different stages in development or growth, and he presents a series of illustrations to substantiate his opinion.

Surgical Treatment of Osseous Cysts.—Von Matolcsy [21] reports on 48 cases of osseous cyst in which operation was performed at the University of Budapest. Curettement and packing with a tibial bone graft were employed in 45 of the cases. In 2 the grafts extruded. Healing occurred in all cases. In children before the cessation of the growth of bone reconstruction of the inserted graft progressed rapidly, identity of the graft in a child of 5½ being almost lost in eight or ten months. In an adult of 24, 2 tibial grafts inserted into the cyst neck of a femur reached approximately the same stage in from two to three years. The author fills the rest of the cavity left after insertion of the bone grafts with fat.

Treatment of Ganglions.—Saegesser [22] reviews the more commonly used forms of treatment for ganglion. Rupture by a blow is not infrequently followed by a recurrence. Surgical extirpation is not a simple office procedure; it leaves a bad scar (unless the transverse incision is used at the wrist) and may also be followed by recurrence. Injection of irritating solutions often leads to recurrence and in addition may result in inflammation of the communicating joints. The recurrence is due to adjacent young cysts. The author recommends multiple punctures as practiced by Budinger. Through a single site in the skin a needle is inserted into the ganglion. Many punctures are made by partially withdrawing the needle each time. The base of the ganglion is particularly well perforated to destroy small growing cysts. The contents of the ganglions are extracted through the needle puncture, and heavy massage is applied to the site of multiple punctures. A pressure

21. von Matolcsy, T.: Ueber die chirurgische Behandlung von Knochencysten, Arch. f. klin. Chir. **185**:175-181, 1936.

22. Saegesser, M.: Die Behandlung der Ganglien, Schweiz. med. Wchnschr. **66**:663-664 (July 11) 1936.

pad is applied for eight days. After two weeks a hard lump remains. No recurrences have been observed by the author.

[ED. NOTE.—The method has been extensively practiced in America. One of the editors has observed recurrences but no more frequently than after excision or injection.]

THE BACK

Sacrarthrogenetic Telalgia.—Pitkin and Pheasant [23] suggest that the term "sciatica" is a poor one to apply to pain originating in the sacrolumbar and sacro-iliac regions. In place of it they would substitute the term "sacrarthrogenetic telalgia." A summary is given of the various points of view concerning the origin of pain low in the back with radiation down the extremity. Dissections on cadavers and on autopsy specimens confirmed Rudinger's observations as to the innervation of the lumbosacral and sacro-iliac articulations. The authors regard pain in the extremity when associated with discomfort low in the back as being a true referred pain and not due to irritation or compression of the trunks of the peripheral nerves. They state that pain is referred from the sacrolumbar zygapophysial articulations to the fourth and fifth lumbar posterior dermatomes; from the sacro-iliac articulation to the fifth lumbar and the first and second sacral posterior dermatomes; from the iliolumbar ligament to all of the five lumbar and first three sacral posterior dermatomes as well as to the first three lumbar anterior dermatomes; from the sacrolumbar and anterior sacro-iliac ligaments to the second and third lumbar anterior dermatomes, and from the posterior sacro-iliac and sacro-ischial ligaments to all of the five lumbar and first three sacral posterior dermatomes as well as the fifth lumbar and first three sacral anterior dermatomes. A study was made of sacral mobility. They found that motion in the sacro-iliac joint can be demonstrated during life and that the amount of motion in the ilia can be measured. In standing, all motion of the trunk, except flexion and extension, are associated with antagonistic movements of the ilia. In males complaining of sacrarthrogenetic pain an increase of one-third in the movement of the ilia was commonly found. The authors devised a special inclinometer to measure this motion. The problem of alternating scoliosis was next considered. They found 22 cases of this condition mentioned in the literature. Sixty-eight examples of alternating scoliosis were found

23. Pitkin, H. C., and Pheasant, H. C.: Sacrarthrogenetic Telalgia: I. Study of Referred Pain, J. Bone & Joint Surg. **18**:111-133, 1936; II. Study of Sacral Mobility, ibid. **18**:365-374, 1936; III. Study of Alternating Scoliosis, ibid. **18**: 706, 1936. Pitkin, H. C.: IV. Differential Diagnosis in Sacrarthrogenetic Scoliosis, ibid. **18**:1008-1017, 1936; V. A Plan for Treatment, ibid. **19**:169-184, 1937.

in 506 examinations for pain low in the back with radiation as described. They believe that the scoliosis was the result of a fixed pathologic position of one or more of the upper sacral joints and that alternation of the scoliosis was caused by a change in the fixed pathologic position of one or more of these joints. The authors state that the sacro-iliac joints may be fixed in one of four pathologic positions: flexion, extension, an increased angle of inclination or a decreased angle of inclination. From these observations and from a statistical analysis of their cases, certain diagnostic postulates were made: 1. If the lumbar portion of the spine is normal, the lumbar curve reflects the position of the sacrum. 2. If the lumbar portion of the spine is normal and the lower extremities equal in length, the lumbar curve normally reflects the pelvic torsion. 3. Transitional sacrarthrogenetic scoliosis reflects the presence of unequal muscular action and denies the presence of sacro-iliac slip. 4. Structural sacrarthrogenetic scoliosis is produced by an iliac slip. 5. Functional sacrarthrogenetic scoliosis is produced by a sacral slip. 6. Secondary patterns of sacrarthrogenetic scoliosis are produced by a combination of slip and strain. Treatment of these disabilities should consist in the restoration of normal alinement in the sacro-iliac joints by relaxation and by manipulation. Normal articular alinement is reached when the back shows the transitional pattern of scoliosis. External support is advocated until normal muscular control is obtained. Where relaxation in the sacral joints persists, arthrodesis is advised.

Roentgen Treatment of Coccygodynia.—Baastrup [24] reports on the treatment of 15 patients with coccygodynia (8 with nontraumatic and 7 with traumatic coccygodynia) by roentgen therapy. Ten were satisfactorily improved (according to the author's standards, "well"). No unpleasant sequelae (premature climacterium) occurred. However, he advises that the treatment be restricted to women past the menopause and to men (whose testes may be shielded during irradiation).

VASCULAR DISORDERS OF THE LIMBS

Vascular Disorders of the Limbs.—A small volume by Thomas Lewis,[25] written particularly for the practitioner and the internist, should be of help also to the orthopedic surgeon who is often faced with functional disturbances resulting from faulty circulation. While nothing relatively new is reported, the book describes in simple language the

24. Baastrup, C. I.: Röntgenbehandlung von Kokzygodynie, Strahlentherapie **56**:184-188, 1936.

25. Lewis, Thomas: Vascular Disorders of the Limbs, New York, The Macmillan Company, 1936.

present concepts of the dynamics and regulation of the circulation and their disturbances in disease. Many simple tests are given which can be carried out in the office without special apparatus. The various forms of treatment are discussed, with the benefit of the author's ripe judgment as to their efficacy.

DUPUYTREN'S CONTRACTURE

Dupuytren's Contracture.—Von Seemen [26] presents photographs of Dupuytren's contracture in a case in which excision of the fascia and involved skin was followed by application of a free flap of skin swung from the dorsum of the ulnar aspect of the hand (Lexer's operation). The author states that 10 patients have been operated on satisfactorily. For a while after operation there is a sense of tightening when a fist is made (glove sensation), but this subsides. The defect on the dorsum apparently cannot always be closed, and pinch grafts may be needed.

Reviewing the material of the clinic of Dr. E. Lexer at Munich, Maurer [27] collects 200 record cases of Dupuytren's contracture. He catalogs the other large series statistically. In his group the lesion was observed three times as often in men as in women. The lesion occurred in 2 patients under 10, in 27 between 40 and 50, in 50 between 50 and 60, in 65 between 60 and 70 and in 27 cases between 70 and 80. One hundred and ten of the patients, or 55 per cent, were hard-working hand laborers. Of the 200 persons afflicted, 49 suffered from muscular articular rheumatism, 18 from sciatica and 12 from gout. Eighteen patients had sustained injuries to the affected extremity. Of these injuries, only 1 involved the hand. Both hands were involved in 107 cases, the right in 52 and the left in 41. Of the 200 patients, in 12, or 6 per cent, the condition presumably had a familial basis.

MISCELLANEOUS

Stenosing Tenovaginitis at the Radial Styloid Process.—Burns and Ellis [28] find that stenosing tenovaginitis at the radial styloid process is more common in women than in men. There is usually a history of several months' increasing painful disability, and a swelling is noted in the line of the abductor pollicis and extensor pollicis brevis muscles. In some cases there is merely thickening of the sheath and in others

26. von Seemen, H.: Zur Operation der Palmarkontraktur (Dupuytrensche Fingerkontraktur), Deutsche Ztschr. f. Chir. **246**:693-696, 1936.

27. Maurer, G.: Zur Lehre der Dupuytrenschen Palmarfascienkontraktur und ihre Behandlung, Deutsche Ztschr. f. Chir. **246**:685-692, 1936.

28. Burns, B. H., and Ellis, V. H.: Stenosing Tendovaginitis at the Radial Styloid Process, Lancet **1**:717-718 (March 28) 1936.

narrowing of the lumen. A partial excision of the sheath with the patient under local anesthesia has been found uniformly satisfactory.

Adhesion of Joints and Injury.—In the opinion of Watson Jones [29] stiffness of a joint after injury is due to adhesions of capsular plications. He states that adhesions following immobilization, if uncomplicated by other factors, recover by the patient's own exercise. This is particularly true of the elbow joint, which should never be subjected to massage or to passive stretching after injury. Other factors that might convert a recoverable stiffness into an irrecoverable stiffness are (*a*) disuse with continued venous stasis, (*b*) recurrent edema and (*c*) continued infection or irritation of foreign bodies near a joint.

Dystrophy of the Fifth Finger.—Thomas [30] reports 3 cases of dystrophy of the terminal phalanx of the fifth finger, which results in shortening and curving of the bone. He suggests that the change is due to osteochondritis. Kirner described this condition.

Hysterical Paralysis.—Myerson [31] reports 6 cases of hysterical paralysis in which cure was obtained by various forms of suggestion. Electrical stimulation of the paralyzed muscles was of use in 2 of the cases. Primary anesthesia followed by directed activity of the patient was resorted to in 2 cases. Assisted motion of the affected member with liberal amounts of suggestion affected recovery in the other 2 cases.

[ED. NOTE.—Hysterical paralysis is not infrequently encountered by the orthopedic surgeon. A careful reading of this article will enable him to understand better the mechanics of production and the rational treatment of these interesting and bizarre states.]

ORTHOPEDIC OPERATIONS

Arthroplasty of the Knee.—Samson [32] reports his results in 37 cases in which arthroplasty of the knee was performed. He has operated in 11 other cases in addition. Approximately one half of the operations were done for ankylosis following gonorrheal infections. All joints were quiescent for at least one year before operation. The usual Putti operation was modified to include construction of a tendon in the center of the joint to prevent lateral displacement of the joint. A free flap of

29. Jones, R. W.: Adhesions of Joints and Injury, Brit. M. J. **1**:925-929 (May 9) 1936.

30. Thomas, A. R.: A New Dystrophy of the Fifth Finger, Lancet **1**:1412-1413 (June 20) 1936.

31. Myerson, A.: Hysterical Paralysis and Its Treatment, J. A. M. A. **105**: 1565-1567 (Nov. 16) 1936.

32. Samson, J. E.: Arthroplasty of the Knee Joint, J. Bone & Joint Surg. **18**:881-892, 1936.

fascia lata is used. Elaborate physical therapy is not considered important, but early weight bearing and the development of muscular strength are emphasized.

Repair of the Ligaments of the Knee.—In a review of 183 cases of derangement of the knee joint, Campbell [33] found evidence of sufficient damage to the ligamentous structures to warrant operative repair in 30. There were 12 cases of rupture of the mesial (internal lateral) ligament and 19 cases of rupture of the anterior crucial ligament. The author describes a new method of repair of the anterior crucial ligament. The joint is exposed through a medial parapatellar incision, and whatever intra-articular repair is necessary is done. A pedicle strip ⅓ inch (0.8 cm.) in diameter and 8 inches (20 cm.) in length is dissected from the quadriceps tendon, capsule and patellar tendon, leaving it attached to the tibial tubercle. A 6 mm. drill hole is then made in the tibia, beginning 1½ inches (3.8 cm.) below the joint line on the anterior internal surface and emerging in the joint just in front of the spine of the tibia at the point of insertion of the anterior crucial ligament. The femur is then drilled, beginning in the intercondylar notch at the point of origin of the anterior crucial ligament and emerging on the lateral aspect of the femur. The free end of the fascia strip is threaded through these holes and securely inclosed in the fascia lata and periosteum after its exposure through a short second incision. The knee is immobilized for three weeks. There was one failure in the 18 cases. Campbell considers the operation simpler and less traumatic than the usual Hey-Groves procedure.

Operation for Ununited Fracture After the Method of Matti.—Matti,[34] of Bern, exposes the site of the ununited fracture and frees all of the contiguous ends of bone except a band (tibia) the width of the finger, posteriorly or laterally (on the femur), which serves to maintain position. The marrow cavity is exposed and chiseled back to bleeding marrow. The edges are freshened. Marrow and spongiosa are removed from the greater trochanter (or from the head of the tibia) and packed carefully between the ends of bone as a bridge from marrow above to similar marrow below. The cortical bone removed in the exposure of the marrow cavities is broken up into tiny pieces and is used to fill the cavity completely. Fixation by wire traction is used if necessary. Weight bearing is deferred until roentgenographic evidence of consolidation has appeared. Since 1926 the author has operated in 25 cases of ununited fracture (of the tibia in 12 cases, the femur in

33. Campbell, W. C.: Repair of Ligaments of Knee, Surg., Gynec. & Obst. **62**:964-968, 1936.

34. Matti, H.: Technic and Resultate meiner Pseudarthrosenoperation, Zentralbl. f. Chir. **63**:1442-1453 (June 20) 1936.

6, the radius in 3, the digital phalanges in 2, the clavicle in 1 and the metatarsus in 1). He obtained spongiosa fifteen times from the greater trochanter (flat approach or hollow chisel). Twenty-three operations have been performed by others. The results of this operation in the author's hands were uniformly successful, even in 2 cases in which infection developed. With the exception of these cases (consolidation in six months), consolidation was obtained in from six to twelve weeks. Of the entire group of 55 cases, union was obtained in 94.5 per cent.

Correction of Equinus.—Kofmann and Wassiliewa [35] contend that the usual tenotomy of the achilles tendon for the correction of equinus leads to permanent muscular weakness. They believe that a gradual correction in both flaccid and spastic paralyses can usually be obtained by gradual redressement. Where the equinus is resistant, a plastic lengthening of the aponeurosis of the gastrocnemius and soleus muscles permits correction of the deformity. This is performed through two lateral incisions at the junction of the upper and the middle third of the calf. The head of the gastrocnemius muscle is retracted posteriorly, and the aponeuroses over both the gastrocnemius and the soleus muscle are cut transversely. Occasionally the iliotibial band must also be incised just above the knees. This permits correction of the deformity. The foot is held in the corrected position in a plaster cast until healing occurs.

Reconstruction of the Digital Tendon Sheath.—Mayer and Ransohoff [36] describe their method for the restoration of the digital tendon sheath by the use of tubes of pyroxylin. The operation is done in two stages. The first consists in transplanting the tube after incision of the scarred tendon with its sheath. The tube is attached proximally and distally to the remaining tendon stump. At the second operation, performed from four to six weeks after the first, the tube is removed, leaving a well formed cellular sheath through which a transplanted piece of tendon is drawn and sewed to the tendon stump proximally and distally. The operative technic is carefully described.

FRACTURES AND DISLOCATIONS

Reversed Colles' Fracture.—Webb and Sheinfeld,[37] from a study of the literature and their own experience, conclude that the relatively rare reversed Colles fracture cannot be reduced successfully by closed

35. Kofmann, V., and Wassiliewa, N.: Die physiologische Korrektur des Spitzfusses, Ztschr. f. Orthop. **65**:226-235, 1936.

36. Mayer, L., and Ransohoff, N.: Reconstruction of Digital Tendon Sheath, J. Bone & Joint Surg. **18**:607-616, 1936.

37. Webb, G., and Sheinfeld, W.: Reversed Colles Fracture with Special Reference to Therapy, J. A. M. A. **104**:2324-2326 (June 29) 1935.

manipulation and advocated open reduction as a routine procedure. Raymer [38] and Bettman and Tannenbaum [39] report 2 cases in which successful closed reduction was accomplished. Postreduction immobilization of the wrist in the neutral or dorsiflexed position was emphasized in both papers.

Conservative Treatment for Habitual Dislocation of the Shoulder.—Davis [40] reports 8 cases of recurrent dislocation of the shoulder, in 6 of which the treatment consisted of adhesive fixation and exercises. The fixation held the arm both forward and in adduction across the chest. Use in this position was permitted. Fixation was applied for two weeks, and exercises were continued for another month. The exercises were given with a view to overdeveloping the internal rotator and abductor muscles. The author offers suggestions as an alternative to operation and not as a substitute.

Dislocation and Fracture; Dislocation of the Elbow.—Biebl [41] reviews 65 cases of dislocation and fracture dislocation of the elbow seen in the clinic of Dr. Lorenz Böhler. In 29 of the cases there was dislocation only, and in the remainder the dislocation was complicated by fracture of varying severity. The most common form of dislocation was posterior and to the radial side. Reduction was obtained by traction and manipulation with the patient under local anesthesia. The arm was then encased in plaster from the phalanges to the axilla, with the elbow at right angles and the forearm midway between pronation and supination. The plaster cast was usually left in place three weeks. The patients returned to work on the average in fifty days. Two had normal function. Myositis ossificans was observed in the brachialis internus muscle. This, the author believes, is due to therapy and is not the result of trauma. In 23 cases roentgenograms taken long after the injury showed ossification in the ligaments and capsule. The roentgenographic picture was normal in only 2 cases after the patient's discharge from the hospital. There were 6 instances in which dislocation was complicated by a tearing off of the medial epicondyle; all but 1 of these were in children. Bony union of the torn epicondyle was found in only 1 case; in spite of fibrous union, good function was obtained in every case. Fracture sprains of the supporting ligaments or of the tip of the olecranon were seen in 4 cases. Myositis ossificans or arthritis deformans was

38. Raymer, J. G.: Reversed Colles Fracture, J. A. M. A. **105**:2150-2151 (Dec. 28) 1935.

39. Bettman, R. B., and Tannenbaum, W. J.: Reverse Colles Fracture—A Plea for Closed Reduction, J. A. M. A. **105**:2151 (Dec. 28) 1935.

40. Davis, A. G.: A Conservative Treatment for Habitual Dislocation of the Shoulder, J. A. M. A. **107**:1012-1015 (Sept. 26) 1936.

41. Biebl, R.: Ueber Endausgänge traumatischer Verrenkungen und Verrenkungsbrüche des Ellbogengelenkes, Arch. f. orthop. u. Unfall-Chir. **37**:55-79, 1936.

not observed in any of these. Treatment of dislocation complicated by fracture was conservative in most instances; the arm was kept in a plaster cast from six to eight weeks. After removal of the plaster cast, active exercises were given. Massage and passive exercises were rarely used. Myositis ossificans was found in only 1 case of dislocation complicated by fracture. Of these 23 patients with fracture and dislocation, 12 have normal motion. Only 2 are still receiving compensation.

Fracture of the Ribs from Cough.—Since 1862, when Gurlt reported 14 cases of fracture of the ribs due to cough, others have reported similar cases, bringing the total to 90. Oechsli [42] made a search for fracture of the ribs in the routine interpretation of 2,000 roentgenograms of the chest and found 11 instances in which from one to four ribs were fractured, an incidence of 0.6 per cent. In all cases the fracture was undoubtedly due to cough. The majority of patients had tuberculosis in the advanced stage. The appearance of the ribs were normal, and healing was prompt. The majority of the fractures were on the right side. The symptoms are typical: During a severe coughing spell a "catch" or "stabbing pain" is felt in a sharply localized area. The position of the fracture line is of considerable interest in relation to the mechanism of fracture. Without exception the fractures were found in a line extending from a point 4 cm. from the costochondral articulation of the fourth rib obliquely downward and laterally to the ninth rib in the midaxillary line. This location corresponds to the heavy muscular attachments of the external oblique muscle, where it interdigitates with the serratus anterior muscle. Anatomic and physiologic evidence indicates that the opposing action of the two sets of muscles, i. e., the serratus muscle against the abdominal muscles, causes these fractures.

Fractures of the Lumbar Transverse Process.—Decoulx and Patoir [43] report that fractures of the lumbar transverse processes are produced either by direct or by indirect violence. In a study of the observations of Chavannaz on 128 cases of fracture they found that 1 process was involved in 35 per cent of the cases, 2 in 29 per cent, 3 in 21 per cent, 4 in 9 per cent, 5 in 3 per cent, 6 in 2 per cent and 7 in 17 per cent. The injury occurred in the first lumbar process in 33 per cent, in the second lumbar process in 48 per cent, in the third lumbar process in 61 per cent and in the fourth lumbar process in 20 per cent. The displacement was always the same, outward and downward. The point is

42. Oechsli, W. R.: Rib Fracture from Cough, J. Thoracic Surg. **5**:530-534, 1936.

43. Decoulx, P., and Patoir, G.: Les fractures des apophyses transverses lombaires, Rev. d'orthop. **23**:97-120, 1936.

emphasized that injury to the soft parts is just as important as the bony lesion and is often responsible for most of the symptoms. The authors divide fractures of the lumbar transverse process into four groups: (1) the common type, (2) the benign type, (3) the masked type and (4) the grave type. In the common type pain is localized to the site of the injury, and no abdominal symptoms are present. Often roentgenograms are the only means of making a diagnosis. Almost no clinical signs are noted in the benign type, which usually consists of fracture of a single process with displacement. In the masked type few symptoms are present at first, the fracture being completely concealed by the presence of other lesions. Symptoms arise when the patient gets up and increase in severity. The symptoms in the grave type are severe. Abdominal rigidity and distention are present. Laparotomy is occasionally performed in cases in which this type of fracture is present. The abdominal symptoms are probably due to retroperitoneal hematoma. The clinical course of these fractures is variable. Isolated fractures may occur without displacement and give rise to few symptoms; in other cases the symptoms are marked. Some fractures with gross displacement give no more trouble than the simple fractures. This discrepancy is explained by a difference in the injury to the soft parts. Treatment consists of recumbency in bed for from two to four weeks. No plaster casts or leather jackets are used. Operation and removal of the fragment done either early or late are frowned on except in rare cases in which there is definite evidence of involvement of the nerve roots.

Treatment of Unreduced Dislocation of the Ankle.—Padovani [44] discusses in detail the treatment of old unreduced dislocations of the ankle accompanying malunited fractures about the ankle joint. He classifies the deformities in four groups: dislocations of the ankle backward, forward, inward and outward. These are the result of malleolar (or bimalleolar) fractures, supramalleolar fractures, epiphysial displacements and comminuted fractures of the lower end of the tibia. Treatment is discussed under the following headings: 1. Osteotomy at the site of fracture. This procedure is chiefly performed on one or on both malleoli. 2. Supramalleolar osteotomy. This operation is usually performed for supramalleolar fractures in which the ankle mortice itself is intact, but it is not necessarily performed at the exact site of injury. 3. Resection of the lower end of the tibia. This is done after comminuted injuries, and the aim is simply to place the astragalus in line with the tibia, irrespective of motion obtained. 4. Astragalectomy. This is performed only when none of the other methods seem applicable.

44. Padovani, M. P.: Traitement des cals vicieux du cou-de-pied, Rev. d'orthop. **23**:441-489, 1936.

5. Arthrodesis of the ankle joint. This is used as an alternative to astragalectomy in selected cases.

[ED. NOTE.—A brief summary cannot do justice to this excellent, well illustrated article dealing with individual and difficult problems.]

End-Results of Fracture of the Distal Tibial Epiphysis.—Aitken,[45] from a study of 21 cases of injury to the lower tibial epiphysis, concludes that the type of injury to the epiphysis determines whether or not there will be subsequent disturbance of growth. He found that crushing of, or fracture through, the epiphysis usually results in a disturbance of growth even when the replacement of the epiphysis is perfect. Complete separation of the epiphysis from the diaphysis does not result in such disturbance even if replacement is not accurate.

RESEARCH

Interaction of Bone and Various Metals.—The interaction between bone and various metals has been investigated by Jones and Lieberman.[46] They found that vanadium steel and nickel-free rustless steel tacks were badly corroded both in bone and in Ringer's solution. High nickel and low nickel rustless steel tacks showed minimal corrosion, and much less bone reaction occurred about them than about any other alloys tested. The authors propose the hypothesis that the intensity of reaction of bone is directly proportional to the chemical changes that occur in the metal with which it is in contact. The question of whether a metal is irritating when buried in living tissue may be solved by immersing it in Ringer's solution; if it remains unchanged there it will probably do the same in vivo.

[ED. NOTE.—This work is of fundamental importance to all surgeons who use metal fixation material. The ordinary vanadium steel plates and screws cause marked irritative reaction and should be discarded in favor of alloys such as high or low nickel rustless steel, which are relatively nonirritating.]

Pathologic-Anatomic Investigation of the Cause of Osteogenesis Imperfecta.—Winkelmann[47] studied the histologic bone sections of a child who died of an infection of the respiratory tract while afflicted with osteogenesis imperfecta. He concludes that osteogenesis is imperfect in the sense that it is delayed but not impossible—simply incomplete. He draws the practical conclusion that if such children are protected

45. Aitken, A. P.: End Results of Fractured Distal Tibial Epiphysis, J. Bone & Joint Surg. **18**:685-691, 1936.

46. Jones, L., and Lieberman, B. A., Jr.: Interaction of Bone and Various Metals: Vanadium Steel and Rustless Steel, Arch. Surg. **32**:990 (June) 1936.

47. Winkelmann, K. L.: Pathologisch-anatomische Untersuchungen über das Wesen der Osteogenesis imperfecta, Ztschr. f. Kinderh. **58**:1-22, 1936.

from intercurrent infections of the respiratory tract they may be carried over the dangerous first years of life to become normal children.

[ED. NOTE.—No personal observations by the author are given to support such optimism. The editors have observed a greatly lessened tendency to fracture in the bones of these children after puberty.]

Distribution of Tension in the Neck of the Femur.—Küntscher [48] subjected the upper two thirds of a femur to pressure and measured the bending of the shaft at different levels with an instrument devised by Okhuizen. He found that the forces were not distributed uniformly, following instead definite paths. The paths are traced through the neck of the femur. The absolute elasticity of the bone substance is substantiated by measurement. Measurement in two axes is essential, for in the neck of the femur forces develop which are at right angles to each other. The author's curves are interesting. The absolute figures are not yet satisfactorily determined.

48. Küntscher, G.: Die Spannungsverteilung am Schenkelhals, Arch. f. klin. Chir. **185**:308-321, 1936.